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Art Unit: 1645 Phone (308) 9347 Serial Number: 10/081,170
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To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: _____

Inventors (please provide full names): YOSHIHIRO KAWAOKA

_____

Earliest Priority Date: 02-23-01

Search Topic:
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known.

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(FILE 'HCAPLUS' ENTERED AT 15:28:32 ON 18 DEC 2003)

L1 1 SEA FILE=REGISTRY ABB=ON PLU=ON "N-ACETYLNEURAMINIC ACID"/CN

L2 1 SEA FILE=REGISTRY ABB=ON PLU=ON "N-GLYCOLYLNEURAMINIC ACID"/CN

L3 2 SEA FILE=REGISTRY ABB=ON PLU=ON L1 OR L2

L4 22557 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 OR SIALIC OR N(W)(ACETYLNEURAMINIC OR GLYCOLYLNEURAMINIC OR (ACETYL OR AC OR GLYCOLYL)(W)(NEU OR NEURAMINIC)) OR NEUNAC OR NEUGC

L5 8360 SEA FILE=HCAPLUS ABB=ON PLU=ON L4 AND CELL

L6 1426 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 AND (MAMMAL? OR SWINE OR PIG OR PIGLET OR HOG OR BOVINE OR OX OR COW OR CATTLE OR OX OR OXEN OR MONKEY OR SIMIAN OR APE OR CHIMP OR CHIMPANZ? OR CANINE OR DOG OR MDCK? OR MADIN DARBY OR MINK OR AVIAN OR BIRD)

L30 44 SEA FILE=HCAPLUS ABB=ON PLU=ON L6 AND MUTAT?

L31 16 SEA FILE=HCAPLUS ABB=ON PLU=ON L30 AND INFLUENZ?

L32 8 L31 NOT L8

L32 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2002:937303 HCAPLUS

DOCUMENT NUMBER: 138:20443

TITLE: Endocrine disruptor screening using DNA chips of endocrine disruptor-responsive genes

INVENTOR(S): Kondo, Akihiro; Takeda, Takeshi; Mizutani, Shigetoshi; Tsujimoto, Yoshimasa; Takashima, Ryokichi; Enoki, Yuki; Kato, Ikunoshin

PATENT ASSIGNEE(S): Takara Bio Inc., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 386 pp.
CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2002355079	A2	20021210	JP 2002-69354	20020313

PRIORITY APPLN. INFO.:
JP 2001-73183 A 20010314
JP 2001-74993 A 20010315
JP 2001-102519 A 20010330

AB A method and kit for detecting endocrine-disrupting chems. using DNA microarrays are claimed. The method comprises preparing a nucleic acid sample containing mRNAs or cDNAs originating in **cells**, tissues, or organisms which have been brought into contact with a sample containing the endocrine disruptor. The nucleic acid sample is hybridized with DNA microarrays having genes affected by the endocrine disruptor or DNA fragments originating in these genes have been fixed. The results obtained are then compared with the results obtained with the control sample to select the gene affected by the endocrine disruptor. Genes whose expression is altered by tri-Bu tin, 4-octaphenol, 4-nonylphenol, di-N-Bu phthalate, dichlorohexyl phthalate, octachlorostyrene, benzophenone, diethylhexyl phthalate, diethylstilbestrol (DES), and 17-β estradiol (E2), were found in mice by DNA chip anal.

L32 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:472264 HCAPLUS
DOCUMENT NUMBER: 137:122132
TITLE: **Influenza** resistance to zanamivir generated in ferrets
AUTHOR(S): Herlocher, M. Louise; Fenton, Rob; Merry, Andrew; Elias, Stephanie; Monto, Arnold S.
CORPORATE SOURCE: Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI, 48109-2029, USA
SOURCE: International Congress Series (2001), 1219(Options for the Control of Influenza IV), 863-877
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Zanamivir (4-Guanidino-2,4-dideoxy-2,3-dehydro-**N-acetylneuraminic** acid), an anti-neuraminidase drug, is highly effective in the treatment of **influenza**. **Influenza** resistance to zanamivir has proved difficult to raise. Two neuraminidase **mutations** leading to resistance in vitro have been identified in several viruses-glu 119 gly and arg 292 lys. Only one resistant virus (an **influenza** B clone) has been observed in vivo in an immunocompromised child. This series of expts. sought to develop A/LA/1/87 (H3N2) **influenza** clones resistant to zanamivir in a ferret model. Using this model resistance to amantadine was easily developed within 6 days of treatment. Although most ferrets treated with zanamivir shed virus in the nasal wash, all ferrets were protected from fever and illness when treated with zanamivir. When ferrets were infected with nasal wash from ferrets previously infected with A/LA/1/87 (H3N2) and treated with zanamivir, 20 clones from their nasal wash grew on **MDCK cells** in the presence of 1 μM zanamivir. Sequencing of the NA genes of these clones revealed no **mutations** at positions 119 or 292. However, a nucleotide **mutation** at position 685 was observed in five of the clones. Sequencing of HA1 and HA2 for all genes is underway. Although characterization of the 20 clones is not complete, we can say that resistance to zanamivir will not arise as quickly or with the same frequency as does resistance to amantadine.
REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:240511 HCAPLUS
DOCUMENT NUMBER: 135:18442
TITLE: Adaptation of **influenza** A viruses to **cells** expressing low levels of **sialic** acid leads to loss of neuraminidase activity
AUTHOR(S): Hughes, Mark T.; McGregor, Martha; Suzuki, Takashi; Suzuki, Yasuo; Kawaoka, Yoshihiro
CORPORATE SOURCE: Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI, 53706, USA

SOURCE: Journal of Virology (2001), 75(8), 3766-3770
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Influenza** A viruses possess two virion surface proteins, hemagglutinin (HA) and neuraminidase (NA). The HA binds to sialyloligosaccharide viral receptors, while the NA removes **sialic** acids from the host **cell** and viral sialyloligosaccharides. Alterations of the HA occur during adaptation of **influenza** viruses to new host species, as in the 1957 and 1968 **influenza** pandemics. To gain a better understanding of the contributions of the HA and possibly the NA to this process, we generated **cell** lines expressing reduced levels of the **influenza** virus receptor determinant, **sialic** acid, by selecting **Madin-Darby canine** kidney **cells** resistant to a lectin specific for **sialic** acid linked to galactose by α(2-3) or α(2-6) linkages. One of these **cell** lines had less than 1/10 as much **N-acetylneuraminic** acid as its parent **cell** line. When serially passaged in this **cell** line, human H3N2 viruses lost sialidase activity due to a large internal deletion in the NA gene, without alteration of the HA gene. These findings indicate that NA **mutations** can contribute to the adaptation of **influenza** A virus to new host environments and hence may play a role in the transmission of virus across species.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:884534 HCAPLUS
DOCUMENT NUMBER: 134:206457

TITLE: Change in Receptor-Binding Specificity of Recent Human **Influenza** A Viruses (H3N2): A Single Amino Acid Change in Hemagglutinin Altered Its Recognition of Sialyloligosaccharides

AUTHOR(S): Nobusawa, E.; Ishihara, H.; Morishita, T.; Sato, K.; Nakajima, K.
CORPORATE SOURCE: Department of Virology, Medical School, Nagoya City University, Mizuho-cho, Mizuho-ku, Nagoya City, 467-8601, Japan

SOURCE: Virology (2000), 278(2), 587-596
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human H3N2 **influenza** A viruses were known to preferentially bind to **sialic** acid (SA) in α2,6Gal linkage on red blood **cells** (RBC). However, H3N2 viruses isolated in **MDCK cells** after 1992 did not agglutinate chicken RBC (CRBC). Expts. with point-**mutated** hemagglutinin (HA) of A/Aichi/51/92, one of these viruses, revealed that an amino acid change from Glu to Asp at position 190 (E190D) was responsible for the loss of ability to bind to CRBC. A/Aichi/51/92 did not agglutinate CRBC treated with

α2,3-sialidase, suggesting that SAα2,3Gal on CRBC might not inhibit the binding of the virus to SAα2,6Gal on CRBC. However, the virus agglutinated derivatized CRBC resialylated with SAα2,6Galβ1,4GlcNAc. These findings suggested that the E190D change might have rendered the HA able to distinguish sialyloligosaccharides on the derivatized CRBC containing the SAα2,6Galβ1,4GlcNAc sequence from those on the native CRBC. (c) 2000 Academic Press.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2000:678571 HCAPLUS

DOCUMENT NUMBER: 133:332449

TITLE: Recognition of **N-glycolylneuraminic** acid linked to galactose by the α2,3 linkage is associated with intestinal replication of **influenza** A virus in ducks

AUTHOR(S): Ito, Toshihiro; Suzuki, Yasuo; Suzuki, Takashi; Takada, Ayato; Horimoto, Taisuke; Wells, Krisna; Kida, Hiroshi; Otsuki, Koichi; Kiso, Makoto; Ishida, Hideharu; Kawaoka, Yoshihiro

CORPORATE SOURCE: Department of Veterinary Public Health, Faculty of Agriculture, Tottori University, Tottori, 680-8553, Japan

SOURCE: Journal of Virology (2000), 74(19), 9300-9305
CODEN: JOVIAM; ISSN: 0022-538X

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The hemagglutinin (HA) of H3 human **influenza** viruses does not support viral replication in duck intestine despite its **avian** origin. A Leu-to-Gln **mutation** at position 226 and a Ser-to-Gly **mutation** at position 228 in the HA of human A/Udorn/307/72 (H3N2) permit a reassortant virus [human Udorn HA, with all other genes from A/mallard/New York/6750/78 (H2N2)] to replicate in ducks. To understand the mol. basis of this change in host range restriction, the authors investigated the receptor specificity of duck **influenza** viruses as well as of human-duck virus reassortants. The results indicate that the recognition of a glycoconjugate moiety possessing **N-glycolylneuraminic** acid (**NeuGc**) linked to galactose by the α2,3 linkage (**NeuGc**.alpha.2,3Gal) is associated with viral replication in duck intestine. Immunofluorescence assays with **NeuGc**.alpha.2,3Gal-specific antiserum detected this moiety primarily on the crypt epithelial **cells** of duck colon. Such recognition, together with biochem. evidence of **NeuGc** in crypt **cells**, correlated exactly with the ability of the virus to replicate in duck colon. These results suggest that recognition of the **NeuGc**.alpha.2,3-Gal moiety plays an important role in the enterotropism of **avian influenza** viruses.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:370705 HCAPLUS
DOCUMENT NUMBER: 131:182223
TITLE: Effects of egg-adaptation on the receptor-binding properties of human **influenza** A and B viruses
AUTHOR(S): Gambaryan, A. S.; Robertson, J. S.; Matrosovich, M. N.
CORPORATE SOURCE: M. P. Chumakov Institute of Poliomyelitis and Viral Encephalitides, Russian Academy of Medical Sciences, Moscow, 142782, Russia
SOURCE: Virology (1999), 258(2), 232-239
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Propagation of human **influenza** viruses in embryonated chicken eggs (CE) results in the selection of variants with amino acid substitutions near the receptor-binding site of the hemagglutinin (HA) mol. To evaluate the mechanisms by which these substitutions enable human virus growth in CE, we studied the binding of 10 human **influenza** A (H1N1, H3N2) and B strains, isolated and propagated solely in **MDCK cells**, and of their egg-adapted counterparts to prepns. of cellular membranes, gangliosides, sialylglycoproteins, and sialyloligosaccharides. All egg-adapted variants differed from nonadapted strains by increased binding to the plasma membranes of chorio-allantoic (CAM) **cells** of CE and by the ability to bind to CAM gangliosides. In addition, there was no decrease in affinity for inhibitors within allantoic fluid. These findings indicate that growth of human **influenza** viruses in CE is restricted because of their inefficient binding to receptors on CAM **cells** and that gangliosides can play an important role in virus binding and/or penetration. The effects of the egg-adaptation substitutions on the receptor-binding properties of the viruses include (i) enhancement of virus binding to the terminal Sia(α2-3)Gal determinant (substitutions in HA positions 190, 225 of H1N1 strains and in position 186 of H3N2 strains); (ii) a decrease of steric interference with more distant parts of the Sia(α2-3Gal)-containing receptors (a loss of glycosylation sites in positions 163 of H1 HA and 187 of type B HA); and (iii) enhanced ionic interactions with the neg. charged mols. due to charged substitutions at the tip of the HA [187, 189, 190 (H1), and 145, 156 (H3)]. Concomitantly with enhanced binding to Sia(α2-3)Gal-terminated receptors, all egg-adapted variants decreased their affinity for equine macroglobulin, a glycoprotein bearing terminal 6'-sialyl(N-acetyllactosamine)-moieties. (c) 1999 Academic Press.

IT **131-48-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(effects of egg adaptation on receptor-binding properties of human **influenza** A and B viruses)

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L32 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:185285 HCAPLUS

DOCUMENT NUMBER: 126:274582
TITLE: Differences in **sialic** acid-galactose linkages in the chicken egg amnion and allantois influence human **influenza** virus receptor specificity and variant selection
AUTHOR(S): Ito, Toshihiro; Suzuki, Yasuo; Takada, Ayato; Kawamoto, Ayumi; Otsuki, Koichi; Masuda, Hiroyuki; Yamada, Mika; Suzuki, Takashi; Kida, Hiroshi; Kawaoka, Yoshihiro
CORPORATE SOURCE: Dep. Disease Control, Grad. Sch. Vet. Med., Sapporo, 060, Japan
SOURCE: Journal of Virology (1997), 71(4), 3357-3362
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human **influenza** viruses are more efficiently isolated by inoculating patient samples into the amniotic rather than the allantoic cavity of embryonated chicken eggs. This type of cultivation selects virus variants with **mutations** around the hemagglutinin (HA) receptor binding site. To understand the mol. basis of these phenomena, the abundances of **sialic** acid (SA) linked to galactose (Gal) by the α-2,3 linkage (SAα2,3Gal) and SAαa2,6Gal in egg amniotic and allantoic **cells** and in **Madin-Darby canine** kidney (**MDCK**) **cells** was investigated. Using SA-Gal linkage-specific lectins (Maackia amurensis agglutinin specific for SAα2,6Gal and Sambucus nigra agglutinin specific for SAα2,3Gal), SAα2,3Gal was found in both allantoic and amniotic **cells** and SAα2,6Gal in only the amniotic **cells**. **MDCK cells** contained both linkages. To investigate how this difference in abundances of SAα2,3Gal and SAα2,6Gal in allantoic and amniotic **cells** affects the appearance of host **cell** variants in eggs, the receptor specificities and HA amino acid sequences of 2 different patient viruses which were isolated and passaged in the amnion or in the allantois and were determined and compared with **MDCK cell**-grown viruses. The viruses maintained high SAα2,6Gal specificities when grown in **MDCK cells** or following ≤2 amniotic passages; however, further passages in either the amnion or allantois resulted in the acquisition of, or a complete shift to, SAα2,3Gal specificity, depending on the virus strain. This change in receptor specificity was accompanied by the appearance of variants in the population with Leu-to-Gln **mutations** at position 226 in their HA. These findings suggest that lack of SAα2,6Gal linkages in the allantois of chicken eggs is a selective pressure for the appearance of host **cell** variants with altered receptor specificities and amino acid changes at position 226.

L32 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1993:598549 HCAPLUS
DOCUMENT NUMBER: 119:198549
TITLE: Alterations of the stalk of the **influenza** virus neuraminidase: deletions and insertions
AUTHOR(S): Luo, Guangxiang; Chung, Jeffrey; Palese, Peter
CORPORATE SOURCE: Microbiol. Dep., Mount Sinai Sch. Med., New

York, NY, 10029, USA
SOURCE: Virus Research (1993), 29(2), 141-53
CODEN: VIREDF; ISSN: 0168-1702
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The neuraminidase (NA) of **influenza** viruses cleaves **sialic** acids from receptors, prevents self-aggregation and facilitates release of virus during budding from host **cells**. Although the structure and function of the globular head of the **influenza** virus NA has been well studied, much less is known about the stalk of the NA, the region between the viral membrane and the globular head. Applying a reverse genetics system, the authors altered the stalk of the **influenza** A/WSN/33 virus NA by making deletions, insertions and **mutations** in this region of the gene. The authors' data show that the length of the NA stalk can be variable. Deletions of up to 28 amino acids and insertions of up to 41 amino acids in the stalk region did not abolish formation of infectious progeny virus. The data also indicate that the cysteine at position 76 is essential for formation of infectious virus, and that deletions beyond the cysteine did not result in infectious virus. Interestingly, shortening of the length of the stalk region by 28 amino acids resulted in a virus with a markedly reduced growth rate in **MDCK cells** as compared to that in MDBK **cells**. An insertion of 41 extra amino acids into the stalk did not significantly interfere with viral growth in **MDCK** or MDBK **cells**, which suggests that the stalk region would tolerate the introduction of long foreign sequences.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, PHIC, PHIN, TOXCENTER, CABA, AGRICOLA, VETU, VETB' ENTERED AT 15:29:45 ON 18 DEC 2003)

L33 120 S L11 AND MUTAT?
L34 52 S L33 AND INFLUENZ?
L35 17 S L34 NOT L13
L36 9 DUP REM L35 (8 DUPLICATES REMOVED)

L36 ANSWER 1 OF 9 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2001166411 MEDLINE
DOCUMENT NUMBER: 21165286 PubMed ID: 11264365
TITLE: Adaptation of **influenza** A viruses to cells expressing low levels of **sialic** acid leads to loss of neuraminidase activity.
AUTHOR: Hughes M T; McGregor M; Suzuki T; Suzuki Y; Kawaoka Y
CORPORATE SOURCE: Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, Wisconsin 53706, USA.
SOURCE: JOURNAL OF VIROLOGY, (2001 Apr) 75 (8) 3766-70.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20010417
Entered Medline: 20010412

AB **Influenza** A viruses possess two virion surface proteins, hemagglutinin (HA) and neuraminidase (NA). The HA binds to

sialyloligosaccharide viral receptors, while the NA removes **sialic** acids from the host cell and viral sialyloligosaccarides. Alterations of the HA occur during adaptation of **influenza** viruses to new host species, as in the 1957 and 1968 **influenza** pandemics. To gain a better understanding of the contributions of the HA and possibly the NA to this process, we generated **cell** lines expressing reduced levels of the **influenza** virus receptor determinant, **sialic** acid, by selecting **Madin-Darby canine** kidney **cells** resistant to a lectin specific for **sialic** acid linked to galactose by alpha(2-3) or alpha(2-6) linkages. One of these cell lines had less than 1/10 as much **N-acetylneuraminic** acid as its parent cell line. When serially passaged in this cell line, human H3N2 viruses lost sialidase activity due to a large internal deletion in the NA gene, without alteration of the HA gene. These findings indicate that NA **mutations** can contribute to the adaptation of **influenza** A virus to new host environments and hence may play a role in the transmission of virus across species.

L36 ANSWER 2 OF 9 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2001556252 MEDLINE
DOCUMENT NUMBER: 21488933 PubMed ID: 11601919
TITLE: Hemagglutinin residues of recent human A(H3N2) **influenza** viruses that contribute to the inability to agglutinate chicken erythrocytes.
AUTHOR: Medeiros R; Escriou N; Naffakh N; Manuguerra J C; van der Werf S
CORPORATE SOURCE: Unite de Genetique Moleculaire des Virus Respiratoires, URA 1966 CNRS, Institut Pasteur, 75724 Paris Cedex 15, France.
SOURCE: VIROLOGY, (2001 Oct 10) 289 (1) 74-85. Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011017
Last Updated on STN: 20020122
Entered Medline: 20011205

AB To identify the molecular determinants contributing to the inability of recent human **influenza** A(H3N2) viruses to agglutinate chicken erythrocytes, phenotypic revertants were selected upon passage in eggs or **MDCK cells**. The Leu194Ile or Val226Ile substitutions were detected in their hemagglutinin (HA) sequence concomitantly with the phenotypic reversion. Remarkably, as little as 3.5% of variants bearing a Val226Ile substitution was found to confer the ability to agglutinate chicken erythrocytes to the virus population. Hemadsorption assays following transient expression of **mutated** HA proteins showed that the successive Gln226 --> Leu --> Ile --> Val changes observed on natural isolates resulted in a progressive loss of the ability of the HA to bind chicken erythrocytes. The Val226Ile change maintained the preference of the HA for SAalpha2,6Gal over SAalpha2,3Gal and enhanced binding of the HA to alpha2,6Gal receptors present on chicken erythrocytes. In contrast, simultaneous Ser193Arg and Leu194Ile substitutions that were found

to confer the ability to agglutinate sheep erythrocytes increased the affinity of the HA for SAalpha2,3Gal.

L36 ANSWER 3 OF 9 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 3
ACCESSION NUMBER: 2000358485 EMBASE
TITLE: Recognition of **N-glycolylneuraminic** acid linked to galactose by the α2,3 linkage is associated with intestinal replication of **influenza** A virus in ducks.
AUTHOR: Ito T.; Suzuki Y.; Suzuki T.; Takada A.; Horimoto T.; Wells K.; Kida H.; Otsuki K.; Kiso M.; Ishida H.; Kawaoka Y.
CORPORATE SOURCE: Y. Kawaoka, Dept. of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, 2015 Linden Dr. West, Madison, WI 53706, United States. kawaokay@svm.vetmed.wisc.edu
SOURCE: Journal of Virology, (2000) 74/19 (9300-9305). Refs: 37
ISSN: 0022-538X CODEN: JOVIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The hemagglutinin (HA) of H3 human **influenza** viruses does not support viral replication in duck intestine despite its **avian** origin. A Leu-to-Gln **mutation** at position 226 and a Ser-to-Gly **mutation** at position 228 in the HA of human A/Udorn/307/72 (H3N2) permit a reassortant virus [human Udorn HA, with all other genes from A/mallard/New York/6750/78 (H2N2)] to replicate in ducks. To understand the molecular basis of this change in host range restriction, we investigated the receptor specificity of duck **influenza** viruses as well as of human-duck virus reassortants. The results indicate that the recognition of a glycoconjugate moiety possessing N-glycolneuramic acid (**NeuGc**) linked to galactose by the α2,3 linkage (**NeuGc**.alpha.2,3Gal) is associated with viral replication in duck intestine. Immunofluorescence assays with **NeuGc** α2,3Gal-specific antiserum detected this moiety primarily on the crypt epithelial **cells** of duck colon. Such recognition, together with biochemical evidence of **NeuGc** in crypt **cells**, correlated exactly with the ability of the virus to replicate in duck colon. These results suggest that recognition of the **NeuGc**.alpha.2,3-Gal moiety plays an important role in the enterotropism of **avian** **influenza** viruses.

L36 ANSWER 4 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 4
ACCESSION NUMBER: 2001:50175 BIOSIS
DOCUMENT NUMBER: PREV200100050175
TITLE: Change in receptor-binding specificity of recent human **influenza** A viruses (H3N2): A single amino acid change in hemagglutinin altered its recognition of sialyloligosaccharides.
AUTHOR(S): Nobusawa, E. [Reprint author]; Ishihara, H.;

Morishita, T.; Sato, K.; Nakajima, K.
CORPORATE SOURCE: Department of Virology, Medical School, Nagoya City University, Mizuho-cho, Mizuho-ku, Nagoya City, 467-8601, Japan
nobusawa@med.nagoya-cu.ac.jp
SOURCE: Virology, (December 20, 2000) Vol. 278, No. 2, pp. 587-596. print.
CODEN: VIRLAX. ISSN: 0042-6822.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jan 2001
Last Updated on STN: 12 Feb 2002

AB Human H3N2 **influenza** A viruses were known to preferentially bind to **sialic** acid (SA) in alpha2,6Gal linkage on red blood cells (RBC). However, H3N2 viruses isolated in **MDCK cells** after 1992 did not agglutinate chicken RBC (CRBC). Experiments with point-**mutated** hemagglutinin (HA) of A/Aichi/51/92, one of these viruses, revealed that an amino acid change from Glu to Asp at position 190 (E190D) was responsible for the loss of ability to bind to CRBC. A/Aichi/51/92 did not agglutinate CRBC treated with alpha2,3-sialidase, suggesting that SAalpha2,3Gal on CRBC might not inhibit the binding of the virus to SAalpha2,6Gal on CRBC. However, the virus agglutinated derivatized CRBC resialylated with SAalpha2,6Galbeta1,4GlcNAc. These findings suggested that the E190D change might have rendered the HA able to distinguish sialyloligosaccharides on the derivatized CRBC containing the SAalpha2,6Galbeta1,4GlcNAc sequence from those on the native CRBC.

L36 ANSWER 5 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:372167 BIOSIS
DOCUMENT NUMBER: PREV200000372167
TITLE: Development of a sensitive chemiluminescent neuraminidase assay for the determination of **influenza** virus susceptibility to zanamivir.
AUTHOR(S): Buxton, Rachel C. [Reprint author]; Edwards, Brooks; Juo, Rouh R.; Voyta, John C.; Tisdale, Margaret; Bethell, Richard C.
CORPORATE SOURCE: Enzyme Pharmacology, Glaxo Wellcome Research, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK
SOURCE: Analytical Biochemistry, (May 1, 2000) Vol. 280, No. 2, pp. 291-300. print.
CODEN: ANBCA2. ISSN: 0003-2697.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 30 Aug 2000
Last Updated on STN: 8 Jan 2002

AB Determination of the sensitivity of **influenza** viruses to neuraminidase (NA) inhibitors is presently based on assays of NA function because, unlike available cell culture methods, the results of such assays are predictive of susceptibility in vivo. At present the most widely used substrate in assays of NA function is the fluorogenic reagent 2'-O-(4-methylumbelliferyl)-**N-acetylneuraminic** acid (MUN). A rapid assay with improved sensitivity is required because a proportion of clinical isolates has insufficient NA to be detectable in the current fluorogenic

assay, and because some **mutations** associated with resistance to NA inhibitors reduce the activity of the enzyme. A chemiluminescence-based assay of NA activity has been developed that uses a 1,2-dioxetane derivative of **sialic** acid (NA-STAR) as the substrate. When compared with the fluorogenic assay, use of the NA-STAR substrate results in a 67-fold reduction in the limit of detection of the NA assay, from 200 pM (11 fmol) NA to 3 pM (0.16 fmol) NA. A panel of isolates from phase 2 clinical studies of zanamivir, which were undetectable in the fluorogenic assay, was tested for activity using the NA-STAR substrate. Of these 12 isolates with undetectable NA activity, 10 (83%) were found to have detectable NA activity using the NA-STAR substrate. A comparison of sensitivity to zanamivir of a panel of **influenza** A and B viruses using the two NA assay methods has been performed. IC50 values for zanamivir using the NA-STAR were in the range 1.0-7.5 nM and those for the fluorogenic assay in the range 1.0-5.7 nM (n = 6). The NA-STAR assay is a highly sensitive, rapid assay of **influenza** virus NA activity that is applicable to monitoring the susceptibility of **influenza** virus clinical isolates to NA inhibitors.

L36 ANSWER 6 OF 9 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 97214021 MEDLINE
DOCUMENT NUMBER: 97214021 PubMed ID: 9060710
TITLE: Differences in **sialic** acid-galactose linkages in the chicken egg amnion and allantois influence human **influenza** virus receptor specificity and variant selection.
AUTHOR: Ito T; Suzuki Y; Takada A; Kawamoto A; Otsuki K; Masuda H; Yamada M; Suzuki T; Kida H; Kawaoka Y
CORPORATE SOURCE: Department of Disease Control, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, Japan.
CONTRACT NUMBER: AI33898 (NIAID)
SOURCE: JOURNAL OF VIROLOGY, (1997 Apr) 71 (4) 3357-62. Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U77831; GENBANK-U77832; GENBANK-U77833; GENBANK-U77834; GENBANK-U77835; GENBANK-U77836; GENBANK-U77837; GENBANK-U77838; GENBANK-U77839; GENBANK-U77840
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970424
Last Updated on STN: 19990129
Entered Medline: 19970411

AB Human **influenza** viruses are more efficiently isolated by inoculating patient samples into the amniotic rather than the allantoic cavity of embryonated chicken eggs. This type of cultivation selects virus variants with **mutations** around the hemagglutinin (HA) receptor binding site. To understand the molecular basis of these phenomena, we investigated the abundances of **sialic** acid (SA) linked to galactose (Gal) by the alpha-2,3 linkage (SA alpha2,3Gal) and SA alpha2,6Gal in egg amniotic and allantoic **cells** and in **Madin-Darby canine** kidney (**MDCK**) **cells**

virus resulting in the change of the conserved Glu 119 (which lies in a pocket beneath the active site of the enzyme) to Gly thus eliminating an electrostatic interaction with the C-4 guanidinium moiety of the inhibitor. **Mutations** (Asn-->Ser) at amino acids 145 and 150 were also found in the hemagglutinin gene of the B/HK/8/73 (HG) virus resistant to 4-guanidino-Neu5Ac2en. No changes were found in the hemagglutinin gene of the resistant A/NWS-G70c virus.

L36 ANSWER 8 OF 9 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1993:507559 BIOSIS
DOCUMENT NUMBER: PREV199396131566
TITLE: Alterations of the stalk of the **influenza** virus neuraminidase: Deletions and insertions.
AUTHOR(S): Luo, Guangxiang; Chung, Jeffrey; Palese, Peter [Reprint author]
CORPORATE SOURCE: Microbiol. Dep., Mount Sinai Sch. Med., One Gustave L. Levy Place, New York, NY 10029, USA
SOURCE: Virus Research, (1993) Vol. 29, No. 2, pp. 141-153. CODEN: VIREDF. ISSN: 0168-1702.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Nov 1993
Last Updated on STN: 6 Nov 1993

AB The neuraminidase (NA) of **influenza** viruses cleaves **sialic** acids from receptors, prevents self-aggregation and facilitates release of virus during budding from host cells. Although the structure and function of the globular head of the **influenza** virus NA has been well studied, much less is known about the stalk of the NA, the region between the viral membrane and the lobular head. Applying a reverse genetics system, we altered the stalk of the **influenza** A/WSN/33 virus NA by making deletions, insertions and **mutations** in this region of the gene. Our data show that the length of the NA stalk can be variable. Deletions of up to 28 amino acids and insertions of up to 41 amino acids in the stalk region did not abolish formation of infectious progeny virus. The data also indicate that the cysteine at position 76 is essential for formation of infectious virus, and that deletions beyond the cysteine did not result in infectious virus. Interestingly, shortening of the length of the stalk region by 28 amino acids resulted in a virus with a markedly reduced growth rate in **MDCK cells** as compared to that in MDBK **cells**. An insertion of 41 extra amino acids into the stalk did not significantly interfere with viral growth in **MDCK** or MDBK **cells**, which suggests that the stalk region would tolerate the introduction of long foreign sequences.

L36 ANSWER 9 OF 9 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 86115409 MEDLINE
DOCUMENT NUMBER: 86115409 PubMed ID: 3003392
TITLE: Variant **influenza** virus hemagglutinin that induces fusion at elevated pH.
AUTHOR: Doms R W; Gething M J; Henneberry J; White J; Helenius A
CONTRACT NUMBER: AI18582 (NIAID)
AI19630 (NIAID)
SOURCE: JOURNAL OF VIROLOGY, (1986 Feb) 57 (2) 603-13.

Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198602
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19860228

AB The hemagglutinin (HA) glycoprotein of **influenza** virus performs two critical roles during infection: it binds virus to cell surface **sialic** acids, and under mildly acidic conditions it induces fusion of the virion with intracellular membranes, liberating the genome into the cytoplasm. The pH dependence of fusion varies for different **influenza** virus strains. Here we report the isolation and characterization of a naturally occurring variant of the X31 strain that fuses at a pH 0.2 units higher than the parent strain does and that is less sensitive to the effects of ammonium chloride, a compound known to elevate endosomal pH. The bromelain-solubilized ectodomain of the variant HA displayed a corresponding shift in the pH at which it changed conformation and bound to liposomes. Cloning and sequencing of the variant HA gene revealed amino acid substitutions at three positions in the polypeptide. Two substitutions were in antigenic determinants in the globular region of HA1, and the third occurred in HA2 near the base of the molecule. By using chimeric HA molecules expressed in CV-1 **cells** from **simian** virus 40-based vectors, we demonstrated that the change in HA2 was solely responsible for the altered fusion phenotype. This substitution, asparagine for aspartic acid at position 132, disrupted a highly conserved interchain salt bridge between adjacent HA2 subunits. The apparent role of this residue in stabilizing the HA trimer is consistent with the idea that the trimer dissociates at low pH. Furthermore, the results demonstrate that **influenza** virus populations contain fusion variants, raising the possibility that such variants may play a role in the evolution of the virus.

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18dec03 15:19:43 User219783 Session D1983.2

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S7 1441 S1 AND (MAMMAL? OR SWINE OR PIG? ? OR PIGLET? ? OR HOG? ? -OR BOVINE OR OX OR OXEN OR COW? ? OR CATTLE OR MONKEY OR SIMI-AN OR APE? ? OR CHIMP? ? OR CHIMPANZ? OR CANINE OR DOG? ? OR -MDCK? OR MADIN(W)DARBY OR MINK OR AVIAN OR BIRD? ?)(10...
S8 466 S7 AND (MUTANT? ? OR MUTAT? OR MUTAGEN? OR POLYMORPH? OR P-OLY(W)(MORPHIS? OR MORPHIC?))
S9 140 S8 AND INFLUENZ?

S12 112 S8 AND INFLUENZ?(3N)VIRUS?
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S17 45 RD S13 (unique items)

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17/3,AB/1 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal
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13910320 PASCAL No.: 99-0091248
Characterization of human **influenza virus** variants selected in vitro in the presence of the neuraminidase inhibitor GS 4071
TAI C Y; ESCARPE P A; SIDWELL R W; WILLIAMS M A; LEW W; HUIWEI WU; KIM C U; MENDEL D B
Research VirologyGilead Sciences, Inc., Foster City, California 94404, United States; Institute for Antiviral Research, Utah State University, Logan, Utah 84322-5600, United States; Medicinal Chemistry, Gilead Sciences, Inc., Foster City, California 94404, United States

Searcher : Shears 308-4994

Journal: Antimicrobial agents and chemotherapy, 1998, 42 (12) 3234-3241
Language: English

An oral prodrug of GS 4071, a potent and selective inhibitor of influenza neuraminidases, is currently under clinical development for the treatment and prophylaxis of **influenza virus** infections in humans. To investigate the potential development of resistance during the clinical use of this compound, variants of the human influenza A/Victoria/3/75 (H3N2) virus with **reduced** susceptibility to the neuraminidase inhibitor GS 4071 were selected in vitro by passaging the virus in **MDCK cells** in the presence of inhibitor. After eight passages, variants containing two amino acid substitutions in the hemagglutinin (A28T in HA1 and R124M in HA2) but no changes in the neuraminidase were isolated. These variants exhibited a 10-fold reduction in susceptibility to GS 4071 and zanamivir (GG167) in an in vitro plaque reduction assay. After 12 passages, a second variant containing these hemagglutinin **mutations** and a Lys substitution for the conserved Arg292 of the neuraminidase was isolated. The **mutant** neuraminidase enzyme exhibited high-level (30,000-fold) resistance to GS 4071, but only moderate (30-fold) resistance to zanamivir and 4-amino-Neu5Ac2en, the amino analog of zanamivir. The **mutant** enzyme had weaker affinity for the fluorogenic substrate 2'-(4-methylumbelliferyl)- alpha -D-**N-acetylneuraminic** acid and lower enzymatic activity compared to the wild-type enzyme. The viral variant containing the **mutant** neuraminidase did not replicate as well as the wild-type virus in culture and was 10,000-fold less infectious than the wild-type virus in a mouse model. These results suggest that although the R292K neuraminidase **mutation** confers high-level resistance to GS 4071 in vitro, its effect on viral virulence is likely to render this **mutation** of limited clinical significance.

17/3,AB/2 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal

13595447 PASCAL No.: 98-0299780
Generation and characterization of a **mutant** of **influenza** A **virus** selected with the neuraminidase inhibitor BCX-140
BANTIA S; GHATE A A; ANANTH S L; SUDHAKAR BABU Y; AIR G M; WALSH G M
BioCryst Pharmaceuticals, Inc., Birmingham, Alabama 35244, United States; Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma 73190, United States; Department of Microbiology, University of Alabama, Birmingham, Alabama 35294, United States
Journal: Antimicrobial agents and chemotherapy, 1998, 42 (4) 801-807
Language: English

Influenza neuraminidase (NA) plays an important role in viral replication, and characterization of viruses resistant to NA inhibitors will help elucidate the role of active-site residues. This information will assist in designing better inhibitors targeted to essential active-site residues that cannot generate drug-resistant **mutations** . In the present study we used the benzoic acid-based inhibitor BCX-140 to select and characterize resistant viruses. BCX-140 binds to the NA active site in an orientation that is opposite that of a **sialic** acid-based compound, 4-guanidino-2,4-dideoxy-2,3-dehydro-**N-acetylneuraminic** acid (GANA). Thus, the guanidino group of BCX-140 binds to Glu-276, whereas in GANA the guanidino group binds to Glu-119. We passaged influenza

A/Singapore/1/57 (H2N2) in **Madin-Darby canine** kidney **cells** in the presence of BCX-140, and virus resistant to this inhibitor was selected after six passages. The NA of this **mutant** was still sensitive to inhibition by BCX-140. However, the **mutant** virus was resistant to BCX-140 in plaque and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays. Sequence analysis of hemagglutinin (HA) and NA genes revealed changes in both, although none were in the active site of the NA. Depending on the method of selection of the resistant virus, two types of changes associated with the **sialic** acid binding site were seen in the HA. One is a change in HA1 of Ala-133 to Thr, a residue close to the binding site, while the other change was Arg-132 of HA1 to Gln, which in HA1 of serotype H3 is a **sialic** acid contact (Asn-137). Binding studies revealed that both types of resistant viruses had **reduced** receptor binding affinity compared to that of the wild type. Thus, resistance to BCX-140 was generated by modifying the HA. NA active-site residue 276 may be essential for activity, and thus, it cannot be changed to generate resistance. However, drug-induced changes in the HA can result in a virus that is less dependent on NA activity for growth in cells and, hence, resistant to NA inhibitors.

17/3,AB/3 (Item 1 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

14789019 Document Delivery Available: 000178304800003 References: 41
TITLE: Characterization of 2 influenza A(H3N2) clinical isolates with **reduced** susceptibility to neuraminidase inhibitors due to **mutations** in the hemagglutinin gene
AUTHOR(S): Abed Y; Bourgault AM; Fenton RJ; Morley PJ; Gower D; Owens IJ; Tisdale M; Boivin G (REPRINT)
AUTHOR(S) E-MAIL: Guy.Boivin@crchul.ulaval.ca
CORPORATE SOURCE: CHU Laval, Res Ctr Infect Dis, Rm RC-709,2705 Blvd Laurier/Quebec City/PQ G1V 4G2/Canada/ (REPRINT); CHU Laval, Res Ctr Infect Dis, /Quebec City/PQ G1V 4G2/Canada/; Univ Laval, /Quebec City/PQ/Canada/; CHUM St Luc, /Montreal/PQ/Canada/; GlaxoSmithKline, Med Res Ctr, /Stevenage/Herts/England/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF INFECTIOUS DISEASES, 2002, V186, N8 (OCT 15), P 1074-1080
GENUINE ARTICLE#: 598YK
PUBLISHER: UNIV CHICAGO PRESS, 1427 E 60TH ST, CHICAGO, IL 60637-2954 USA
ISSN: 0022-1899
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Previous studies have shown that amino acid changes in the hemagglutinin (HA) gene of **influenza viruses** may result in **decreased** susceptibility to neuraminidase inhibitors (NAIs) in vitro. However, the emergence and characteristics of such HA variants in the clinical setting remain poorly studied. Herein, we report 2 influenza A(H3N2) isolates, from untreated patients, harboring an Arg229-->Ile substitution in the HA1 gene. The Ile229 variants were as sensitive as the Arg229 viruses to zanamivir and oseltamivir in neuroaminidase inhibition assays but were significantly less susceptible (by 60-140-fold) in **cell**-based assays. Although the Ile229 variants adsorbed less efficiently to **Madin-Darby canine** kidney (**MDCK**)

cells in kinetic binding assays, they remained very sensitive to zanamivir in ferrets. Our study shows the importance of the HA1 229 residue in virus binding to **MDCK cells** and confirms the unreliability of **cell**-based assays in predicting the in vivo susceptibility of HA variants to NAIs.

17/3,AB/4 (Item 2 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

13545763 Document Delivery Available: 000174091100003 References: 153
TITLE: Loss of **N-glycolylneuraminic** acid in humans: Mechanisms, consequences, and implications for hominid evolution
AUTHOR(S): Varki A (REPRINT); Ruff C
CORPORATE SOURCE: Univ Calif San Diego, Glycobiol Res & Training Ctr, /La Jolla//CA/92093 (REPRINT); Univ Calif San Diego, Glycobiol Res & Training Ctr, /La Jolla//CA/92093; Univ Calif San Diego, Dept Med, /La Jolla//CA/92093; Univ Calif San Diego, Dept Cellular & Mol Med, /La Jolla//CA/92093
PUBLICATION TYPE: BOOK IN SERIES
PUBLICATION: YEARBOOK OF PHYSICAL ANTHROPOLOGY, VOL 44, 2001, V44, P54-69
GENUINE ARTICLE#: BT80Z
BOOK SERIES TITLE: YEARBOOK OF PHYSICAL ANTHROPOLOGY
PUBLISHER: WILEY-LISS, INC, 605 THIRD AVE, NEW YORK, NY 10158-0012 USA
ISBN: **********
ISSN: 0096-848X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: The surface of all **mammalian cells** is covered with a dense and complex array of sugar chains, which are frequently terminated by members of a family of molecules called **sialic** acids. One particular **sialic** acid called **N-glycolylneuraminic** acid (Neu5Gc) is widely expressed on most **mammalian** tissues, but is not easily detectable on human **cells**. In fact, it provokes an immune response in adult humans. The human deficiency of Neu5Gc is explained by an inactivating **mutation** in the gene encoding CMP-**N-acetylneuraminic** acid hydroxylase, the rate-limiting enzyme in generating Neu5Gc in **cells** of other **mammals**. This deficiency also results in an excess of the precursor **sialic** acid **N-acetylneuraminic** acid (Neu5Ac) in humans. This **mutation** appears universal to modem humans, occurred sometime after our last common ancestor with the great apes, and happens to be one of the first known human-great ape genetic differences with an obvious biochemical readout. While the original selection mechanisms and major biological consequences of this human-specific **mutation** remain uncertain, several interesting clues are currently being pursued. First, there is evidence that the human condition can explain differences in susceptibility or resistance to certain microbial pathogens. Second, the functions of some endogenous receptors for **sialic** acids in the immune system may be altered by this difference. Third, despite the lack of any obvious alternate pathway for synthesis, Neu5Gc has been reported in human tumors and possibly in human fetal tissues, and traces have even been detected in normal human tissues. One possible explanation is that this represents accumulation of Neu5Gc from dietary sources of animal origin. Finally, a markedly **reduced** expression of hydroxylase in the brains of other mammals raises the possibility that the human-specific **mutation** of this enzyme could have played a role in human brain evolution. Yrbk Phys

Anthropol 44:54-69, 2001. (C) 2001 Wiley-Liss, Inc.

17/3,AB/5 (Item 3 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

12553933 References: 29
TITLE: Adaptation of **influenza** A **viruses** to cells expressing low levels of **sialic** acid leads to loss of neuraminidase activity
AUTHOR(S): Hughes MT; McGregor M; Suzuki T; Suzuki Y; Kawaoka Y (REPRINT)
AUTHOR(S) E-MAIL: kawaokay@svm.vetmed.wisc.edu
CORPORATE SOURCE: Univ Wisconsin, Dept Pathobiol Sci, 2015 Linden Dr W/Madison//WI/53706 (REPRINT); Univ Wisconsin, Dept Pathobiol Sci, /Madison//WI/53706; Univ Tennessee, Dept Pathol, /Memphis//TN/38163; Univ Shizouka, Dept Biochem, /Shizuoka 4228526//Japan/; Univ Tokyo, Inst Med Sci, /Tokyo 1088639//Japan/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF VIROLOGY, 2001, V75, N8 (APR), P3766-3770
GENUINE ARTICLE#: 414QN
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
ISSN: 0022-538X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: **Influenza** A **viruses** possess two virion surface proteins, hemagglutinin (HA) and neuraminidase (NA). The HA binds to sialyloligosaccharide viral receptors, while the NA removes **sialic** acids from the host cell and viral sialyloligosaccarides. Alterations of the HA occur during adaptation of **influenza viruses** to new host species, as in the 1957 and 1968 influenza pandemics. To gain a better understanding of the contributions of the HA and possibly the NA to this process, we generated cell lines expressing **reduced** levels of the **influenza virus** receptor determinant, **sialic** acid, by selecting **Madin-Darby canine** kidney **cells** resistant to a lectin specific for **sialic** acid linked to galactose by alpha (2-3) or alpha (2-6) linkages, One of these cell lines had less than 1/10 as much **N-acetylneuraminic** acid as its parent cell line. When serially passaged in this cell line, human H3N2 viruses lost sialidase activity due to a large internal deletion in the NA gene, without alteration of the HA gene. These findings indicate that NA **mutations** can contribute to the adaptation of **influenza** A **virus** to new host environments and hence may play a role in the transmission of virus across species.

17/3,AB/6 (Item 4 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

11838966 References: 55
TITLE: **Influenza virus** infection of desialylated cells
AUTHOR(S): Stray SJ; Richard RD; Air GM (REPRINT)
CORPORATE SOURCE: Univ Oklahoma, Dept Biochem & Mol Biol, BMSB 840,ROB 26901/Oklahoma City//OK/73190 (REPRINT); Univ Oklahoma, Dept Biochem & Mol Biol, /Oklahoma City//OK/73190; Univ Alabama, Microbiol Grad Program, /Birmingham//AL/35294
PUBLICATION TYPE: JOURNAL

PUBLICATION: GLYCOBIOLOGY, 2000, V10, N7 (JUL), P649-658
GENUINE ARTICLE#: 338QD
PUBLISHER: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND
ISSN: 0959-6658
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: **Sialic** acid has long been considered to be the sole receptor for **influenza virus**. The viral hemagglutinin (HA) is known to bind cell surface **sialic** acid, and **sialic** acids on viral glycoproteins are cleaved by the viral neuraminidase (NA) to promote efficient release of progeny virus particles. However, NWS-Mvi, a **mutant** virus completely lacking NA, grows well in **MDCK cells** continuously treated with exogenous neuraminidase (sialidase), Exogenous sialidase quantitatively releases all **sialic** acids from purified glycoproteins and glycolipids of **MDCK cells** and efficiently removes surface **sialic** acid from intact **cells**, Binding of NWS-Mvi and parent **influenza viruses** to **MDCK cells** is indistinguishable, and is only partially **reduced** by sialidase treatment of the cells, Both **mutant** and wild-type viruses enter enzymatically desialylated cells and initiate transcription. The ability of **influenza** A reassortant **viruses** to infect desialylated cells is shared by recent H3N2 clinical isolates, suggesting that this may be a general property of **influenza** A **viruses**. We propose that **influenza virus** infection can result from **sialic** acid-independent receptors, either directly or in a multistage process. When **sialic** acid is present, it may act to enhance virus binding to the cell surface to increase interaction with secondary receptors to mediate entry. Understanding virus entry will be critical to further efforts in infection control and prevention.

17/3,AB/7 (Item 5 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

11759288 References: 40
TITLE: Interdependence of hemagglutinin glycosylation and neuraminidase as regulators of **influenza virus** growth: a study by reverse genetics
AUTHOR(S): Wagner R; Wolff T; Herwig A; Pleschka S; Klenk HD (REPRINT)
AUTHOR(S) E-MAIL: Klenk@mailer.uni-marburg.de
CORPORATE SOURCE: Univ Marburg, Inst Virol, Postfach 2360/D-35011 Marburg//Germany/ (REPRINT); Univ Marburg, Inst Virol, /D-35011 Marburg//Germany/; Univ Giessen, Inst Mikrobiol & Mol Biol, /D-35392 Giessen//Germany/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF VIROLOGY, 2000, V74, N14 (JUL), P6316-6323
GENUINE ARTICLE#: 327WU
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
ISSN: 0022-538X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: The hemagglutinin (HA) of fowl plague virus A/FPV/Rostock/34 (H7N1) carries two N-linked oligosaccharides attached to Asn123 and Asn149 in close vicinity to the receptor-binding pocket. In previous studies in which HA **mutants** lacking either one (**mutants** G1 and G2) or both (**mutant** G1,2) glycosylation sites had been expressed from a simian

virus 40 vector, we showed that these glycans regulate receptor binding affinity (M, Ohuchi, R. Ohuchi, A. Feldmann, and H. D. Klenk, J. Virol, 71:8377-8384, 1997). We have now investigated the effect of these **mutations** on virus growth using recombinant viruses generated by an RNA polymerase I-based reverse genetics system. Two reassortants of **influenza virus** strain A/WSN/33 were used as helper viruses to obtain two series of HA **mutant** viruses differing only in the neuraminidase (NA), Studies using N1 NA viruses revealed that loss of the oligosaccharide from Asn149 (**mutant** G2) or loss of both oligosaccharides (**mutant** G1,2) has a pronounced effect on virus growth in **MDCK cells**. Growth of virus lacking both oligosaccharides from infected **cells** was retarded, and virus yields in the medium were **decreased** about 20-fold. Likewise, there was a reduction in plaque size that was distinct with G1,2 and less pronounced,vith G2, These effects could be attributed to a highly impaired release of **mutant** progeny viruses from host cells. In contrast, with recombinant viruses containing N2 NA, these restrictions were much less apparent. N1 recombinants showed lower neuraminidase activity than N2 recombinants, indicating that N2 NA is able to partly overrule the high-affinity binding of **mutant** HA to the receptor. These results demonstrate that N-glycans flanking the receptor binding site of the HA molecule are potent regulators of **influenza virus** growth, with the glycan at Asn149 being dominant and that at Asn123 being less effective. In addition, we show here that HA and NA activities need to be highly balanced in order to allow productive **influenza virus** infection.

17/3,AB/8 (Item 6 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

11610113 References: 33
TITLE: **Influenza** A **viruses** lacking sialidase activity can undergo multiple cycles of replication in cell culture, eggs, or mice
AUTHOR(S): Hughes MT; Matrosovich M; Rodgers ME; McGregor M; Kawaoka Y (REPRINT)
AUTHOR(S) E-MAIL: kawaokay@svm.vetmed.wisc.edu
CORPORATE SOURCE: Univ Wisconsin, Dept Pathobiol Sci, 2015 Linden Dr W/Madison//WI/53706 (REPRINT); Univ Wisconsin, Dept Pathobiol Sci, /Madison//WI/53706; Univ Tennessee, Dept Pathol, /Memphis//TN/38163; St Jude Childrens Res Hosp, Dept Virol & Mol Biol, /Memphis//TN/38105; MP Chumakov Inst Poliomyelitis & Viral Encephalit, /Moscow 142782//Russia/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF VIROLOGY, 2000, V74, N11 (JUN), P5206-5212
GENUINE ARTICLE#: 312MX
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
ISSN: 0022-538X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: **Influenza** A **viruses** possess both hemagglutinin (HA), which is responsible for binding to the terminal **sialic** acid of sialyloligosaccharides on the cell surface, and neuraminidase (NA), which contains sialidase activity that removes **sialic** acid from sialyloligosaccharides. Interplay between HA receptor-binding and NA receptor-destroying sialidase activity appears to be important for replication of the virus. Previous studies by others have shown that

influenza A **viruses** lacking sialidase activity can undergo multiple cycles of replication if sialidase activity is provided exogenously. To investigate the sialidase requirement of **influenza viruses** further, we generated a series of sialidase-deficient **mutants**. Although their growth was less efficient than that of the parental NA-dependent virus, these viruses underwent multiple cycles of replication in cell culture, eggs, and mice. To understand the molecular basis of this viral growth adaptation in the absence of sialidase activity, we investigated changes in the HA receptor-binding affinity of the sialidase-deficient **mutants**, The results show that **mutations** around the HA receptor-binding pocket **reduce** the virus's affinity for cellular receptors, compensating for the loss of sialidase, Thus, sialidase activity is not absolutely required in the **influenza** A **virus** life cycle but appears to be necessary for efficient virus replication.

17/3,AB/9 (Item 7 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

11167052 References: 31
TITLE: Zanamivir susceptibility monitoring and characterization of **influenza virus** clinical isolates obtained during phase II clinical efficacy studies
AUTHOR(S): Barnett JM; Cadman A; Gor D; Dempsey M; Walters M; Candlin A; Tisdale M (REPRINT); Morley PJ; Owens IJ; Fenton RJ; Lewis AP; Claas ECJ; Rimmelzwaan GF; De Groot R; Osterhaus ADME
AUTHOR(S) E-MAIL: smt40154@glaxowellcome.co.uk
CORPORATE SOURCE: Glaxo Wellcome Med Res Ctr, Clin Virol Unit, /Stevenage/Herts/England/ (REPRINT); Glaxo Wellcome Med Res Ctr, Clin Virol Unit, /Stevenage/Herts/England/; Glaxo Wellcome Med Res Ctr, Syst Biol Unit, /Stevenage/Herts/England/; Glaxo Wellcome Med Res Ctr, Adv Technol & Informat Unit, /Stevenage/Herts/England/; Univ Hosp Dijkzigt, Sophia Childrens Hosp, /NL-3015 GD Rotterdam//Netherlands/; Erasmus Univ, /Rotterdam//Netherlands/
PUBLICATION TYPE: JOURNAL
PUBLICATION: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 2000, V44, N1 (JAN), P 78-87
GENUINE ARTICLE#: 266EN
PUBLISHER: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171 USA
ISSN: 0066-4804
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Zanamivir is a highly selective neuraminidase (NA) inhibitor with demonstrated clinical efficacy against **influenza** A and B **virus** infections. In phase II clinical efficacy trials (NAIB2005 and NAIB2008), virological substudies showed mean reductions in virus shedding after 24 h of treatment of 1.5 to 2.0 log(10) 50% tissue culture infective doses compared to a placebo, with no reemergence of virus after the completion of therapy. Paired isolates (n = 41) obtained before and during therapy dth zanamivir demonstrated no shifts in susceptibility to zanamivir when measured by NA assays, although far a few isolates NA activity was too low to evaluate. In plaque reduction assays in **MDCK cells**, the susceptibility of isolates to zanamivir was extremely variable even at baseline and did not correlate with the speed of resolution of virus shedding. Isolates with apparent limited susceptibility to zanamivir by plaque reduction proved highly susceptible in vivo in the ferret model.

Further sequence analysis of paired isolates revealed no changes in the hemagglutinin and NA genes in the majority of isolates. The few changes observed were all natural variants. No amino acid changes that had previously been identified in vitro as being involved with **reduced** susceptibility to zanamivir were observed. These studies highlighted problems associated with monitoring susceptibility to NA inhibitors in the clinic, in that no reliable cell-based assay is available. At present the NA assay is the best available predictor of susceptibility to NA inhibitors in vivo, as measured in the validated ferret model of infection.

17/3,AB/10 (Item 8 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

08341202 References: 34
TITLE: Catalytic and framework **mutations** in the neuraminidase active site of **influenza viruses** that are resistant to 4-guanidino-Neu5Ac2en
AUTHOR(S): Gubareva LV (REPRINT); Robinson MJ; Bethell RC; Webster RG
CORPORATE SOURCE: ST JUDE CHILDRENS HOSP,DEPT VIROL MOL BIOL, 332 N LAUDERDALE, POB 318/MEMPHIS//TN/38101 (REPRINT); GLAXO WELLCOME RES & DEV LTD,DEPT VIROL/STEVENAGE SG1 2NY/HERTS/ENGLAND/; UNIV TENNESSEE,DEPT PATHOL/MEMPHIS//TN/38163
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF VIROLOGY, 1997, V71, N5 (MAY), P3385-3390
GENUINE ARTICLE#: WT189
PUBLISHER: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171
ISSN: 0022-538X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Here we report the isolation of **influenza virus** A/turkey/Minnesota/833/80 (H4N2) with a **mutation** at the catalytic residue of the neuraminidase (NA) active site, rendering it resistant to the novel NA inhibitor 4-guanidino-Neu5Ac2en (GG167), The resistance of the **mutant** stems from replacement of one of three invariant arginines (Arg 292-->Lys) that are conserved among all viral and bacterial NAs and participate in the conformational change of **sialic** acid moiety necessary for substrate catalysis, The Lys292 **mutant** was selected in vitro after 15 passages at increasing concentrations of GG167 (from 0.1 to 1,000 mu M), conditions that earlier gave rise to GG167-resistant **mutants** with a substitution at the framework residue Glu119, Both types of **mutants** showed similar degrees of resistance in plaque reduction assays, but the Lys292 **mutant** was more sensitive to the inhibitor in NA inhibition tests than were **mutants** bearing a substitution at framework residue 119 (Asp, Ala, or Gly), Cross-resistance to other NA inhibitors (4-amino-Neu5Ac2en and Neu5Ac2en) varied among **mutants** resistant to GG167, being Lowest for Lys292 and highest for Asp119, All GG167-resistant **mutants** demonstrated markedly **reduced** NA activity, only 3 to 50% of the parental level, depending on the particular amino acid substitution, The catalytic **mutant** (Lys292) showed a significant change in pH optimum of NA activity, from 5.9 to 5.3. All of the **mutant** NAs were less stable than the parental enzyme at low pH, Despite their impaired NA activity, the GG167-resistant **mutants** grew as well as parental virus in **Madin-Darby canine** kidney **cells** or in embryonated chicken eggs, However, the infectivity in mice was 500-fold lower for Lys292 than for the parental

virus, These findings demonstrate that amino acid substitution in the NA active site at the catalytic or framework residues, followed by multiple passages in vitro, in the presence of increasing concentrations of the NA inhibitor GG167, generates GG167-resistant viruses with **reduced** NA activity and **decreased** infectivity in animals.

17/3,AB/11 (Item 9 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

07132662 References: 34
TITLE: CHARACTERIZATION OF **MUTANTS** OF **INFLUENZA** A **VIRUS** SELECTED WITH THE NEURAMINIDASE INHIBITOR 4-GUANIDINO-NEU5AC2EN
AUTHOR(S): GUBAREVA LV; BETHELL R; HART GJ; MURTI KG; PENN CR; WEBSTER RG (Reprint)
CORPORATE SOURCE: ST JUDE CHILDRENS HOSP,DEPT VIROL & MOLEC BIOL,332 N LAUDERDALE,POB 318/MEMPHIS//TN/38101 (Reprint); ST JUDE CHILDRENS HOSP,DEPT VIROL & MOLEC BIOL/MEMPHIS//TN/38101; GLAXO RES & DEV LTD,DEPT VIROL/STEVENAGE SG1 2NY/HERTS/ENGLAND/; UNIV TENNESSEE,DEPT PATHOL/MEMPHIS//TN/38163
PUBLICATION: JOURNAL OF VIROLOGY, 1996, V70, N3 (MAR), P1818-1827
GENUINE ARTICLE#: TV696
ISSN: 0022-538X
LANGUAGE: ENGLISH DOCUMENT TYPE: ARTICLE

ABSTRACT: The development of viral resistance to the neuraminidase (NA) inhibitor, 4-guenidino-Neu5Ac2en, of **influenza viruses** was studied by serial passage of A/Turkey/Minnesota/833/80 (H4N2) in **Madin-Darby canine** kidney **cells** in the presence of increasing concentrations of inhibitor, Resistant **mutants**, selected after eight passages, had a 10,000-fold reduction in sensitivity to the inhibitor in plaque assays, but their affinity (1/K-d) to the inhibitor was similar to that of the parental virus, Electron microscopic analysis revealed aggregation of the **mutant** virus at the cell surface in the presence of the inhibitor, Sequence analysis established that a substitution had occurred in the NA (Arg-249 to Lys) and in the HA2 subunit of the hemagglutinin (Gly-75 to Glu), in the vicinity of the proposed second **sialic** acid binding site, The change at residue 249 appears to be a chance **mutation**, for we were unable to reisolate this **mutant**, whereas subsequent experiments indicate changes in the hemagglutinin, After 13 passages of the parental virus, **mutants** that were resistant to the high concentrations of inhibitor tested were obtained, These viruses retained their drug-resistant phenotype even after five passages without the inhibitor, Electron microscopic analysis revealed no aggregation of virus on the surface of infected cells in the presence of the inhibitor, Sequence analysis of the NA gene from these drug-resistant **mutants** revealed an additional substitution of Glu to Ala at the conserved amino acid residue 119, This substitution is responsible for **reducing** the affinity of the inhibitor to the NA. Our findings suggest that the emergence of **mutants** resistant to 4-guanidino-Neu5Ac2en is a multistep process requiring prolonged exposure to the inhibitor.

17/3,AB/12 (Item 10 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

06795008 References: 33
TITLE: THE CATALYTIC TRIAD OF THE **INFLUENZA** C **VIRUS** GLYCOPROTEIN HEF ESTERASE - CHARACTERIZATION BY SITE-DIRECTED **MUTAGENESIS** AND FUNCTIONAL ANALYSIS
AUTHOR(S): PLESCHKA S; KLENK HD; HERRLER G (Reprint)
CORPORATE SOURCE: UNIV MARBURG,INST VIROL,ROBERT KOCH STR 17/D-35037 MARBURG//GERMANY/ (Reprint); UNIV MARBURG,INST VIROL/D-35037 MARBURG//GERMANY/
PUBLICATION: JOURNAL OF GENERAL VIROLOGY, 1995, V76, OCT (OCT), P2529-2537
GENUINE ARTICLE#: RY545
ISSN: 0022-1317
LANGUAGE: ENGLISH DOCUMENT TYPE: ARTICLE

ABSTRACT: **Influenza** C **virus** is able to inactivate its own cellular receptors by virtue of a sialate 9-O-acetylesterase that releases the acetyl residue at position C-9 of N-acetyl-9-O-acetylneuraminic acid (Neu5,9Ac(2)). The receptor-destroying enzyme activity is a function of the surface glycoprotein HEF and this esterase belongs to the class of serine hydrolases. In their active site, these enzymes contain a catalytic triad made up of a serine, a histidine and an aspartic acid residue. Sequence comparison with other serine esterases has indicated that, in addition to serine-71 (S71), the amino acids histidine-368 or -369 (H368/369) and aspartic acid 261 (D261) are the most likely candidates to form the catalytic triad of the **influenza** C **virus** glycoprotein. By site-directed **mutagenesis**, **mutants** were generated in which alanine substituted for either of these amino acids. Using a phagemid expression vector, pSP1D-HEF the HEF gene was expressed in both COS 7 and **MDCK** I **cells**. The glycoprotein was obtained in a functional form only in the latter cells, as indicated by its transport to the cell surface and measurable enzyme activity. The low level of expression could be increased by stimulating the NF-kappa B-binding activity of the cytomegalovirus immediately promoter/enhancer element of the vector. The esterase activity of the **mutant** proteins was compared with that of the wild-type glycoprotein. With Neu5,9Ac(2) as the substrate, the esterase specific activities of the S71/A **mutant** and the H368,369/A **mutant** were **reduced** by more than 90%. In the case of the D261/A **mutant** the specific activity was **reduced** by 64%. From this data we conclude that S71, H368/369 and D261 are likely to represent the catalytic triad of the **influenza** C **virus** glycoprotein KEF. In addition, N280 is proposed to stabilize the oxyanion of the presumptive transition state intermediate formed by the enzyme-substrate complex.

17/3,AB/13 (Item 11 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

04804953 References: 26
TITLE: ALTERATIONS OF THE STALK OF THE **INFLUENZA VIRUS** NEURAMINIDASE - DELETIONS AND INSERTIONS
AUTHOR(S): LUO GX; CHUNG J; PALESE P (Reprint)
CORPORATE SOURCE: CUNY MT SINAI SCH MED,DEPT MICROBIOL,1 GUSTAVE L LEVY PL/NEW YORK//NY/10029 (Reprint); CUNY MT SINAI SCH MED,DEPT MICROBIOL,1 GUSTAVE L LEVY PL/NEW YORK//NY/10029
PUBLICATION: VIRUS RESEARCH, 1993, V29, N2 (AUG), P141-153
GENUINE ARTICLE#: LU414
ISSN: 0168-1702

LANGUAGE: ENGLISH DOCUMENT TYPE: ARTICLE

ABSTRACT: The neuraminidase (NA) of **influenza viruses** cleaves **sialic** acids from receptors, prevents self-aggregation and facilitates release of virus during budding from host cells. Although the structure and function of the globular head of the **influenza virus** NA has been well studied, much less is known about the stalk of the NA, the region between the viral membrane and the globular head. Applying a reverse genetics system, we altered the stalk of the **influenza** A/WSN/33 **virus** NA by making deletions, insertions and **mutations** in this region of the gene. Our data show that the length of the NA stalk can be variable. Deletions of up to 28 amino acids and insertions of up to 41 amino acids in the stalk region did not abolish formation of infectious progeny virus. The data also indicate that the cysteine at position 76 is essential for formation of infectious virus, and that deletions beyond the cysteine did not result in infectious virus. Interestingly, shortening of the length of the stalk region by 28 amino acids resulted in a virus with a markedly **reduced** growth rate in **MDCK cells** as compared to that in MDBK **cells**. An insertion of 41 extra amino acids into the stalk did not significantly interfere with viral growth in **MDCK** or MDBK **cells**, which suggests that the stalk region would tolerate the introduction of long foreign sequences.

17/3,AB/14 (Item 1 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01529391
A method for producing influenza hemagglutinin multivalent vaccines
Methode fur die Produktion von multivalenten Influenza Hamagglutinin Vakzinen
Procede de production de vaccins antigrippaux polyvalents composes d'hemagglutinine
PATENT ASSIGNEE:
MG-PMC, L.L.C., (2245190), Connaught Laboratories, Inc., Route 611, P.O. Box 187, Swiftwater, PA 18370, (US), (Applicant designated States: all)
INVENTOR:
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Wilkinson, Bethanie E., 25 Joseph Circle, Higganum, CT 06441, (US)
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Hackett, Craig Stanway, 94 Kondracki Lane, Wallingford, CT 06492, (US)
LEGAL REPRESENTATIVE:
Harding, Charles Thomas (70742), D. Young & Co. 21 New Fetter Lane, London EC4A 1DA, (GB)
PATENT (CC, No, Kind, Date): EP 1275726 A2 030115 (Basic)
EP 1275726 A3 030226
APPLICATION (CC, No, Date): EP 2002076629 950526;
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
EXTENDED DESIGNATED STATES: LT
RELATED PARENT NUMBER(S) - PN (AN):
EP 833933 (EP 95922133)
INTERNATIONAL PATENT CLASS: C12N-015/86

ABSTRACT EP 1275726 A2

A method of preparing a recombinant influenza vaccine using DNA technology is provided. The resulting vaccine is a multivalent, preferably trivalent, influenza vaccine based on a mixture of recombinant hemagglutinin antigens cloned from **influenza viruses** having epidemic potential. The recombinant hemagglutinin antigens are full length, uncleaved (HAO), glycoproteins produced from baculovirus expression vectors in cultured insect cells and purified under non-denaturing conditions. In the preferred embodiment, the cloned HA genes are then modified by deletion of the natural hydrophobic signal peptide sequences and replacing them with a new baculovirus chitinase signal peptide. A general approach for the efficient extraction and purification of recombinant HA protein produced in insect cells is also disclosed for the purification of rHA proteins from A sub-types and B type **influenza viruses**.

ABSTRACT WORD COUNT: 127

NOTE:
Figure number on first page: 1

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200303	158
SPEC A	(English)	200303	14050
Total word count - document A			14208
Total word count - document B			0
Total word count - documents A + B			14208

17/3,AB/15 (Item 2 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01450394
Monoclonal antibodies to colon cancer antigen
Gegen Colon Krebs Antigen gerichtete monoklonale Antikorper
Anticorps monoclonaux diriges contre des antigenes associes au carcinome du colon
PATENT ASSIGNEE:
CHIRON CORPORATION, (572531), 4560 Horton Street, Emeryville California 94608-2916, (US), (Applicant designated States: all)
INVENTOR:
Ring, David B., 2375 Cowper Street, Palo Alto, CA 94301, (US)
LEGAL REPRESENTATIVE:
Duckworth, Timothy John (75911), J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5JJ, (GB)
PATENT (CC, No, Kind, Date): EP 1241264 A1 020918 (Basic)
APPLICATION (CC, No, Date): EP 2002005019 951128;
PRIORITY (CC, No, Date): US 349489 941202; US 485786 950607
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
RELATED PARENT NUMBER(S) - PN (AN):
EP 794792 (EP 95941489)
INTERNATIONAL PATENT CLASS: C12P-021/08; C07K-002/00; C12N-015/02; A61K-039/00; A61K-039/395

ABSTRACT EP 1241264 A1
A monoclonal antibody which is obtainable from the hybridoma deposited with the American Type Culture Collection having Accession No. HB 11751,

antigen bound by the monoclonal antibody and monoclonal antibodies that bind to the antigen. Use of such antibodies and antigens in the manufacture of medicaments for inducing an immune response or for diagnosing or treating cancer.
ABSTRACT WORD COUNT: 58

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200238	209
SPEC A	(English)	200238	10406
Total word count - document A			10615
Total word count - document B			0
Total word count - documents A + B			10615

17/3,AB/16 (Item 3 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01446343
Self-assembling polynucleotide delivery system
Selbst zusammenbaubares system zur verabreichung von polynukleotiden
SYSTEME DE LIVRAISON D'UN POLYNUCLEOTIDE A ASSEMBLAGE AUTONOME
PATENT ASSIGNEE:
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, (221072), 300 Lakeside Drive, 22nd Floor, Oakland, California 94612-3550, (US), (Applicant designated States: all)
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Szoka, Francis C., Jr., 45 Mendosa Avenue, San Francisco CA 94116, (US)
Haensler, Jean, Aventis Pasteur SA, Campus Merieux, 1541, Avenue Marcel Merieux, 69280 Marcy L'Etoile, (FR)
LEGAL REPRESENTATIVE:
Thiel, Christian, Dr. Dipl.-Chem. (57845), Schneiders & Behrendt Rechts- und Patentanwalte Huestrasse 23 (Westfalenbankgebaude), 44787 Bochum, (DE)
PATENT (CC, No, Kind, Date): EP 1236473 A2 020904 (Basic)
EP 1236473 A3 030115
APPLICATION (CC, No, Date): EP 2002001408 930405;
PRIORITY (CC, No, Date): US 864876 920403; US 913669 920714
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
RELATED PARENT NUMBER(S) - PN (AN):
EP 636028 (EP 93909508)
INTERNATIONAL PATENT CLASS: A61K-038/02; A61K-047/00; C07F-009/10

ABSTRACT EP 1236473 A2
This invention provides a self-assembling polynucleotide delivery system comprising components aiding in the delivery of the polynucleotide to the desired address which are associated via noncovalent interactions with the polynucleotide. The components of this system include DNA-masking components, cell recognition components, charge-neutralization and membrane-permeabilization components, and subcellular localization components. Specific compounds useful in this system are also provided.
ABSTRACT WORD COUNT: 59
NOTE:
Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200236	188
SPEC A	(English)	200236	12065
Total word count - document A			12253
Total word count - document B			0
Total word count - documents A + B			12253

17/3,AB/17 (Item 4 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01432850
Recombinant vectors for producing HCV envelope proteins
Rekombinante Vektoren zur Herstellung von HCV Hullproteinen
Vecteurs recombinants pour la production de proteines d'enveloppe de HCV
PATENT ASSIGNEE:
Innogenetics N.V., (713148), Industriepark Zwijnaarde 7 Box 4, 9052 Zwijnaarde, (BE), (Applicant designated States: all)
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Buyse, Marie-Ange, E. Ronsestraat 23, 9820 Merelbeke, (BE)
LEGAL REPRESENTATIVE:
De Clercq, Ann et al (87754), De Clercq, Brants & Partners, Edgard Gevaertdreef 10a, 9830 Sint-Martens-Latem, (BE)
PATENT (CC, No, Kind, Date): EP 1211315 A1 020605 (Basic)
APPLICATION (CC, No, Date): EP 2002003643 950731;
PRIORITY (CC, No, Date): EP 94870132 940729
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
RELATED PARENT NUMBER(S) - PN (AN):
EP 721505 (EP 95930434)
INTERNATIONAL PATENT CLASS: C12N-015/40; C12N-005/10; C07K-014/18; A61K-039/29; G01N-033/569

ABSTRACT EP 1211315 A1
The present invention relates to a recombinant vectors encoding an HCV envelope E1 and/or E2 and/or E1/E2 protein encoding sequence. The invention also relates to recombinant nucleic acids comprising said HCV protein encoding sequences. The invention further relates to host cells transformed with said recombinant vectors, as well as recombinant HCV proteins expressed by said host cells and use thereof in diagnostic methods or kits or therapeutic or prophylactic methods of treatment of HCV or HCV vaccine compositions.
ABSTRACT WORD COUNT: 79
NOTE:
Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200223	1905
SPEC A	(English)	200223	23297

Total word count - document A 25202
Total word count - document B 0
Total word count - documents A + B 25202

17/3,AB/18 (Item 5 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01387437
PSEUDO-TYPE RETROVIRUS VECTOR CONTAINING MEMBRANE PROTEIN HAVING HEMAGGLUTININ ACTIVITY
MEMBRANPROTEIN MIT HEMAGGLUTENIN-AKTIVITAT BEINHALTENDER RETROVIRUSVEKTOR DES PSEUDOTYPS
VECTEUR DE RETROVIRUS DE PSEUDO-TYPE CONTENANT UNE PROTEINE DE MEMBRANE POSSEDANT UNE ACTIVITE D'HEMAGGLUTININE
PATENT ASSIGNEE:
Dnavec Research Inc., (2324702), 25-11, Kannondai 1-chome, Tsukuba-shi,, Ibaraki 305-0856, (JP), (Applicant designated States: all)
INVENTOR:
YONEMITSU, Yoshikazu, 5-31-3, Najima, Higashi-ku, Fukuoka-shi, Fukuoka 813-0043, (JP)
NAKAJIMA, Toshihiro, 3-1-25, Maruyamadai, Kawanisi-shi, Hyogo 666-0152, (JP)
NAKAMARU, Kenji, 202 Seiwahaitsu, 3-22-17, Minamimagoma, Oota-ku, Tokyo 143-0025, (JP)
KOBAYASHI, Masanori, c/o DSL,Shionogi Co.,Ltd, 2-5-1,Mishima,Settsu-shi, Osaka 566-0022, (JP)
HASEGAWA, Mamoru, c/o DNAVEC Research Inc., 25-11, Kannondai 1-chome, Tukuba-shi, Ibaraki 305-0856, (JP)
UEDA, Yasuji, c/o DNAVEC Research Inc., 25-11, Kannondai 1-chome, Tsukuba-shi, Ibaraki 305-0856, (JP)
IIDA, Akihiro, c/o DNAVEC Research Inc., 25-11, Kannondai 1-chome, Tsukuba-shi, Ibaraki 305-0856, (JP)
SAKAKIBARA, Hiroyuki, c/o DNAVEC Research Inc., 25-11, Kannondai 1-chome, Tsukuba-shi, Ibaraki 305-0856, (JP)
LEGAL REPRESENTATIVE:
Warcoin, Jacques et al (19072), Cabinet Regimbeau, 20, rue de Chazelles, 75847 Paris Cedex 17, (FR)
PATENT (CC, No, Kind, Date): EP 1291419 A1 030312 (Basic)
WO 2001092508 011206
APPLICATION (CC, No, Date): EP 2001936834 010601; WO 2001JP4659 010601
PRIORITY (CC, No, Date): JP 2000169090 000601
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE; TR
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C12N-015/09; C12N-005/10; A61K-035/76; A61K-048/00; C12N-15:09; C12R-1:92; C12N-5:10; C12R-1:91

ABSTRACT EP 1291419 A1
The present invention provides a retroviral vector containing a membrane protein having a hemagglutinin activity. The present inventors constructed a retroviral vector pseudotyped by the membrane protein having a hemagglutinin activity. This viral vector showed gene transfer at a high efficiency into host cells. In particular, it was established that genes can be transferred thereby at a high efficiency into cells into which genes can hardly be transferred by the conventional techniques, for example, blood cells and hematopoietic cells including

hematopoietic stem cells, and mucous cells including mucosa epithelial cells. The viral vector of the present invention is highly useful as a vector for gene therapy.
ABSTRACT WORD COUNT: 107
NOTE:
Figure number on first page: 0003

LANGUAGE (Publication,Procedural,Application): English; English; Japanese
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200311	573
SPEC A	(English)	200311	24345
Total word count - document A			24918
Total word count - document B			0
Total word count - documents A + B			24918

17/3,AB/19 (Item 6 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01372888
NOVEL COLLECTINS
NEUE COLLECTINE
NOUVELLES COLLECTINES
PATENT ASSIGNEE:
FUSO PHARMACEUTICAL INDUSTRIES LTD., (1209242), 7-10, Doshomachi 1-chome, Chuo-ku, Osaka-shi, Osaka 541-0045, (JP), (Applicant designated States: all)
INVENTOR:
WAKAMIYA, Nobutaka, 1-4, Toko-Gojo 10-chome, Asahikawa-shi, Hokkaido 078-8345, (JP)
KESHI, Hiroyuki, 2-25, Tonotsuji 1-chome Sumiyoshi-ku, Osaka-shi Osaka 558-0042, (JP)
OHTANI, Katsuki, SK Hights B, 2-8 Kamui-Nijo 8-chome, Asahikawa-shi Hokkaido 070-8012, (JP)
SAKAMOTO, Takashi, 1138, Shiba, Sakurai-shi, Nara 633-0074, (JP)
KISHI, Yuichiro, 5-53-4, Fukiya-cho, Wakayama-shi, Wakayama 640-8324, (JP)
LEGAL REPRESENTATIVE:
Webber, Philip Michael et al (83441), Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL, (GB)
PATENT (CC, No, Kind, Date): EP 1283214 A1 030212 (Basic)
WO 2001081401 011101
APPLICATION (CC, No, Date): EP 2001922014 010423; WO 2001JP3468 010423
PRIORITY (CC, No, Date): JP 2000120358 000421
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE; TR
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C07K-014/47; C12N-015/12; C12P-021/02; A01K-067/027; C07K-016/18; G01N-033/53

ABSTRACT EP 1283214 A1
Provided are isolated collectin (CL-L2s) genes including a base sequence set out in SEQ ID NO: 1, 3, 5, 7, 9, 12, 36, 38 or 40 relating to a novel collectin which are expected to exhibit an antibacterial activity, an antiviral activity and the like particularly in a human body; and isolated collectin proteins including an amino acid sequence

set out in SEQ ID NO: 2, 4, 6, 8, 10, 13, 37, 39 or 41 and derivatives and fragments thereof.
ABSTRACT WORD COUNT: 81
NOTE:
Figure number on first page: 0004
LANGUAGE (Publication,Procedural,Application): English; English; Japanese
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200307	2603
SPEC A	(English)	200307	20282
Total word count - document A			22885
Total word count - document B			0
Total word count - documents A + B			22885

17/3,AB/20 (Item 7 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01322318
Composition comprising membrane virus subviral target and fusion particles and vaccine comprising said composition
Membranvirus Ziel- und Fusion-subvirale Partikel enthaltende Zusammensetzung und diese enthaltende Impstoff
Composition comprenant des particules sous-virales cibles et fusions de virus enveloppes, et vaccin la contenant
PATENT ASSIGNEE:
Deutsches Krebsforschungszentrum Stiftung des offentlichen Rechts, (577160), Im Neuenheimer Feld 280, 69120 Heidelberg, (DE), (Applicant designated States: all)
INVENTOR:
Bosch, Valerie, Dr., Flussgasse 12, 69245 Bammental, (DE)
Sparacio, Sandra, Wasserturmstr. 39, 69214 Eppelheim, (DE)
Zeilfelder, Udo, Lowenstr.1, 68259 Mannheim, (DE)
Pfeiffer, Tanya, Goethestr. 36, 69221 Dossenheim, (DE)
Henzler, Tanya, Kuhler Grund 22, 69126 Heidelberg, (DE)
LEGAL REPRESENTATIVE:
Schussler, Andrea, Dr. (80502), Kanzlei Huber & Schussler Truderinger Strasse 246, 81825 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 1130089 A1 010905 (Basic)
APPLICATION (CC, No, Date): EP 2000103242 000217;
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C12N-007/04; A61K-039/21; C07K-014/705; C07K-014/715; C07K-014/16

ABSTRACT EP 1130089 A1
Described is a composition of membrane virus subviral particles, preferably retrovirus-like, more preferably HIV-like subparticles, comprising (a) an env-defective, at least one cellular receptor and at least one coreceptor containing membrane virus target particle encoded by an env-defective membrane virus particle encoding vector construct, at least one cellular receptor encoding vector(s) and at least one coreceptor encoding vector(s) and (b) a membrane virus fusion particle encoded by an env-defective membrane virus particle encoding vector construct and an env-encoding vector, wherein said composition of membrane virus subviral particles is capable of inter-membrane virus

particle membrane fusion resulting in the formation of membrane-virus particles. Also described is a vaccine comprising the composition of the present invention.
ABSTRACT WORD COUNT: 115
NOTE:
Figure number on first page: 1

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200136	349
SPEC A	(English)	200136	5596
Total word count - document A			5945
Total word count - document B			0
Total word count - documents A + B			5945

17/3,AB/21 (Item 8 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01292075
Production of vaccines
Vakzinproduktion
Production de vaccins
PATENT ASSIGNEE:
Crucell Holland B.V., (3178570), Archimedesweg 4, 2333 CN Leiden, (NL), (Applicant designated States: all)
INVENTOR:
Pau, Maria Grazia, Kloksteeg 29, 2311 SK Leiden, (NL)
Uytdehaag, Alphonsus Gerardus Cornelius Maria, Park Arenberg 41, 3731 EP De Bilt, (NL)
Schouten, Govert Johan, Da Costastraat 82,, 2321 AR Leiden, (NL)
LEGAL REPRESENTATIVE:
Klein, Bart et al (80366), Crucell Holland B.V., Intellectual Property Department, P.O. Box 2048, 2300 CA Leiden, (NL)
PATENT (CC, No, Kind, Date): EP 1108787 A2 010620 (Basic)
EP 1108787 A3 010829
APPLICATION (CC, No, Date): EP 2000204190 001124;
PRIORITY (CC, No, Date): EP 99203983 991126
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE; TR
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C12N-015/34; C12N-005/10; C07K-014/11; C07K-014/075; C12N-015/85; C12N-007/02; A61K-039/145

ABSTRACT EP 1108787 A2
Novel means and methods are provided for the production of **mammalian** viruses, comprising infecting a culture of immortalized human **cells** with the virus, incubating the culture infected with virus to propagate the virus under conditions that permit growth of the virus, and to form a virus-containing medium, and removing the virus-containing medium.
The viruses can be harvested and be used for the production of vaccines.
Advantages - human cells of the present invention can be cultured under defined serum free conditions, and the cells show improved capability for propagating virus.

In particular, methods are provided for producing in cultured human cells **Influenza virus** and vaccines derived thereof. This method eliminates the necessity to use whole chicken embryos for the production of Influenza vaccines.

The method provides also for the continuous or batchwise removal of culture media. As such, the present invention allows the large scale continuous production of viruses to a high titer.

ABSTRACT WORD COUNT: 154

NOTE:

Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; English

FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200125	1142
SPEC A	(English)	200125	12523
Total word count - document A			13665
Total word count - document B			0
Total word count - documents A + B			13665

17/3,AB/22 (Item 9 from file: 348)

DIALOG(R)File 348:EUROPEAN PATENTS

01270888

NOVEL YEAST VARIANTS AND PROCESS FOR PRODUCING GLYCOPROTEIN CONTAINING MAMMALIAN TYPE SUGAR CHAIN

HEFEVARIANTEN UND VERFAHREN ZUR HERSTELLUNG VON GLYKOPROTEIN ENTHALTENDEN ZUCKERKETTEN VOM SAUGETIERTYP

NOUVELLES VARIANTES DE LEVURE ET PROCEDE DE PRODUCTION DE GLYCOPROTEINE

PATENT ASSIGNEE:

KIRIN BEER KABUSHIKI KAISHA, (579945), 10-1, Shinkawa 2-chome, Chuo-ku, Tokyo 104-8288, (JP), (Applicant designated States: all)

National Institute of Advanced Industrial Science and Technology, (3298251), 3-1, Kasumigaseki 1-chome, Chiyoda-ku, Tokyo 100-8921, (JP), (Applicant designated States: all)

INVENTOR:

Chiba, Yasunori, Kiban Gijutsu Kenkyusho, Kirin Beer K.K., 1-13-5, Fukuura, Kanazawa-ku, Yokohama-shi, Kanagawa 236-0004, (JP)

Kainuma, Mami, Kiban Gijutsu Kenkyusho, Kirin Beer K.K., 1-13-5, Fukuura, Kanazawa-ku, Yokohama-shi, Kanagawa 236-0004, (JP)

Takeuchi, Makoto, Kiban Gijutsu Kenkyusho, Kirin Beer K.K., 1-13-5, Fukuura, Kanazawa-ku, Yokohama-shi, Kanagawa 236-0004, (JP)

Kawashima, Eiko, Kiban Gijutsu Kenkyusho, Kirin Beer K.K., 1-13-5, Fukuura, Kanazawa-ku, Yokohama-shi, Kanagawa 236-0004, (JP)

Yoshida, Satoshi, Kiban Gijutsu Kenkyusho, Kirin Beer K.K., 1-13-5, Fukuura, Kanazawa-ku, Yokohama-shi, Kanagawa 236-0004, (JP)

Yamano, Shigeyuki, Kiban Gijutsu Kenkyusho, Kirin Beer K.K., 1-13-5, Fukuura, Kanazawa-ku, Yokohama-shi, Kanagawa 236-0004, (JP)

Jigami, Yoshifumi, 6-255, Sakae-cho, Ushiku-shi, Ibaraki 300-1233, (JP)

Ishii, Tomoko, 1055-588, Shimohirooka, Tsukuba-shi, Ibaraki 305-0042, (JP)

Shimma, Yoh-ichi, 1-408-301, Azuma, Tsukuba-shi, Ibaraki 305-0031, (JP)

LEGAL REPRESENTATIVE:

HOFFMANN - EITLE (101511), Patent- und Rechtsanwalte Arabellastrasse 4, 81925 Munchen, (DE)

PATENT (CC, No, Kind, Date): EP 1211310 A1 020605 (Basic)

WO 200114522 010301
APPLICATION (CC, No, Date): EP 2000953436 000816; WO 2000JP5474 000816
PRIORITY (CC, No, Date): JP 99233215 990819
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
EXTENDED DESIGNATED STATES: AL; LT; LV; MK; RO; SI
INTERNATIONAL PATENT CLASS: C12N-001/19; C12P-021/02; C12N-1:19; C12R-1:865 ; C12P-21:02; C12R-1:865

ABSTRACT EP 1211310 A1
Provided are novel yeast **mutants** capable of producing a glycoprotein in which a sugar chain, having a sugar chain structure identical to that of a sugar chain produced from **mammalian cells**, is attached to an asparagine residue of a protein; and a process for producing the sugar chain and the glycoprotein by a glycoengineering technique using the **mutants**. The newly-bred auxotrophic triple **mutant** and auxotrophic quadruple **mutant** of the present invention can produce a large quantity of high purity neutral sugar chains identical to the high mannose type sugar chains produced from human and other **mammalian cells** and glycoproteins having the neutral sugar chains. Also, introduction of genes for biosynthesis of a mammalian type sugar chain into the **mutants** enables efficient production of a mammalian type sugar chain of high-mannose type, hybrid-type, complex-type, etc. or a protein having the mammalian type sugar chain.
ABSTRACT WORD COUNT: 144
NOTE:
Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; Japanese
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200223	1326
SPEC A	(English)	200223	16186
Total word count - document A			17512
Total word count - document B			0
Total word count - documents A + B			17512

17/3,AB/23 (Item 10 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01218550
INFLUENZA VIRUS HEMAGGLUTININ-BINDING PEPTIDES
SICH AN DAS HAMAGGLUTININ DES INFLUENZAVIRUS BINDENDES PEPTID
PEPTIDES SE LIANT A L'HEMAGGLUTININE DU VIRUS DE LA GRIPPE
PATENT ASSIGNEE:
OTSUKA PHARMACEUTICAL CO., LTD., (304161), 9, Kandatsukasa-cho 2-chome, Chiyoda-ku Tokyo 101-8535, (JP), (Applicant designated States: all)
INVENTOR:
SATO, Toshinori, 5-4-5-407, Tsunashima Higashi, Kohoku-ku, Yokohama-shi, Kanagawa 223-0052, (JP)
ISHIKAWA, Dai, 3-1-7-102, Kasuga, Tokushima-shi, Tokushima 770-0002, (JP)
TANAKA, Michinori, 42-13, Chidorigahama, Sumiyoshi, Aizumi-cho, Itano-gun, Tokushima 771-1265, (JP)
OGINO, Koichi, 197-3, Aza Higashihama, Minamihama, Muya-cho, Naruto-shi, Tokushima 772-0003, (JP)

TAKI, Takao, 8-4, Aza Sanomiya, Ejiri, Kitajima-cho, Itano-gun, Tokushima 221-0205, (JP)
LEGAL REPRESENTATIVE:
HOFFMANN - EITLE (101511), Patent- und Rechtsanwalte Arabellastrasse 4, 81925 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 1167382 A1 020102 (Basic)
WO 200059932 001012
APPLICATION (CC, No, Date): EP 2000911385 000327; WO 2000JP1867 000327
PRIORITY (CC, No, Date): JP 9991962 990331
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: C07K-007/08; C07K-016/28; A61K-031/00; A61K-038/00

ABSTRACT EP 1167382 A1
In accordance with this invention there is provided an **influenza virus** hemagglutinin-binding peptide having any of the amino acid sequences defined under SEQ ID NO:1 to NO:11. This peptide binds specifically to the hemagglutinin associated with the first step of **influenza virus** infection to prevent binding of the virus to the host receptor and, as such, finds application as a prophylactic drug for **influenza virus** infection or a therapeutic drug for influenza.
ABSTRACT WORD COUNT: 73
NOTE:
Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; Japanese
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200201	669
SPEC A	(English)	200201	12440
Total word count - document A			13109
Total word count - document B			0
Total word count - documents A + B			13109

17/3,AB/24 (Item 11 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

01118328
THERAPEUTIC AGENTS
THERAPEUTISCHE WIRKSTOFFE
AGENTS THERAPEUTIQUES
PATENT ASSIGNEE:
Takara Shuzo Co, Ltd., (710326), 609, Takenaka-cho, Fushimi-ku, Kyoto-shi, Kyoto 612-8061, (JP), (Applicant designated States: all)
INVENTOR:
ENOKI, Tatsuji, 202, Inouehausu 10-23, Nango 1-chome, Otsu-shi Shiga 520-0865, (JP)
TOMONO, Jun, A-106, Takarashuzoshataku 16, Shibukawa Terado-cho, Muko-shi Kyoto 617-0002, (JP)
KOYAMA, Nobuto, 96, Kubo Ogura-cho, Uji-shi Kyoto 611-0042, (JP)
IKAI, Katsushige, 9-421-45, Kibogaokahonmachi Konan-cho, Koka-gun Shiga 520-3332, (JP)
SAGAWA, Hiroaki, 503, Hamoparesu-Kusatsu 2-12-1, Nishishibukawa 2, Kusatsu-shi Shiga 525-0025, (JP)

KATO, Ikunoshin, 1-1-150, Nanryo-cho, Uji-shi Kyoto 611-0028, (JP)
LEGAL REPRESENTATIVE:
Vossius, Volker, Dr. et al (12524), Dr. Volker Vossius, Patentanwaltskanzlei - Rechtsanwaltskanzlei, Holbeinstrasse 5, 81679 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 1086952 A1 010328 (Basic)
WO 9964424 991216
APPLICATION (CC, No, Date): EP 99923961 990608; WO 99JP3058 990608
PRIORITY (CC, No, Date): JP 98175295 980609; JP 98223723 980724; JP 9911639 990120
DESIGNATED STATES: AT; BE; CH; CY; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: C07D-493/08; C07D-309/32; A61K-031/35; A61K-007/00; A23L-001/30; A23L-002/00

ABSTRACT EP 1086952 A1
Therapeutic or preventive agents for diseases requiring apoptosis induction, cancerous diseases, diseases requiring the inhibition of active oxygen production, those requiring the inhibition of nitrogen monoxide production, those requiring the inhibition of prostaglandin synthesis, those requiring the inhibition of synovial cell proliferation, those requiring the induction of heat shock protein production or those requiring the inhibition of (alpha)-glycosidase, which contain as the active ingredient compounds selected from among compounds represented by general formula (I), (wherein X and Y are each H or CH2))OH, provided that when X is CH2))OH, Y is H, while when X is H, Y is CH2))OH), those represented by general formula (II), (wherein R is a residue obtained by freeing a compound having an SH group from the SH group) and salts of both; and foods, drinks, cosmetics and so on, containing compounds selected from among compounds of general formula (I), those of general formula (II) and salts of both.
ABSTRACT WORD COUNT: 155
NOTE:
Figure number on first page: NONE

LANGUAGE (Publication,Procedural,Application): English; English; Japanese
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	200113	787
SPEC A	(English)	200113	18647
Total word count - document A			19434
Total word count - document B			0
Total word count - documents A + B			19434

17/3,AB/25 (Item 12 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00955706
CHO cell sialidase by recombinant DNA technology
Rekombinante CHO Zell Sialidase
Sialidase recombinante de cellule CHO
PATENT ASSIGNEE:
Genentech, Inc., (210486), 1 DNA Way, South San Francisco, CA 94080-4990, (US), (applicant designated states:
AT;BE;CH;DE;DK;ES;FR;GB;GR;IE;IT;LI;LU;MC;NL;PT;SE)
INVENTOR:

Warner, Thomas G., 541 Wellington, San Carlos, CA 94070, (US)
Sliwkowski, Mary B., 42 Oak Creek Lane, San Carlos, CA 94070, (US)
LEGAL REPRESENTATIVE:
Walton, Sean Malcolm et al (77071), MEWBURN ELLIS, York House, 23 Kingsway, London WC2B 6HP, (GB)
PATENT (CC, No, Kind, Date): EP 866130 A1 980923 (Basic)
APPLICATION (CC, No, Date): EP 98106858 940517;
PRIORITY (CC, No, Date): US 62586 930517; US 187327 940125
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
RELATED PARENT NUMBER(S) - PN (AN):
EP 700443 (EP 949167894)
INTERNATIONAL PATENT CLASS: C12N-015/56; C12N-005/06; C12N-015/01; C12N-015/85; C12N-009/24; C12P-021/00;

ABSTRACT EP 866130 A1
A recombinant cell line has a constitutive sialidase whose functional expression is disrupted, for example by homologous recombination or using antisense RNA. Sialidase is purified from cell culture fluid of Chinese hamster ovary cells. DNA encoding sialidase is obtained using an oligonucleotide probe designed using amino acid sequence data on the sialidase, and the DNA is expressed in host cells transformed with the DNA.
ABSTRACT WORD COUNT: 65

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	9839	328
SPEC A	(English)	9839	16913
Total word count - document A			17241
Total word count - document B			0
Total word count - documents A + B			17241

17/3,AB/26 (Item 13 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00878079
INDUCTION OF IMMUNE RESPONSE AGAINST DESIRED DETERMINANTS
DIE ERZEUGUNG EINER IMMUNANTWORT GEGEN ERWUNSCHTE DETERMINANTEN
INDUCTION D'UNE REACTION IMMUNE CONTRE DES DETERMINANTS SOUHAITES
PATENT ASSIGNEE:
Epimmune, Inc., (2493300), 6555 Nancy Ridge Drive, Suite 200, San Diego, California 92121, (US), (Proprietor designated states: all)
INVENTOR:
ALEXANDER, Jeffery, L., 3657 Caminito Cielo Del Mar, San Diego, CA 92130, (US)
DEFREES, Shawn, 540 Avenida Verde, San Marcos, CA 92069, (US)
SETTE, Alessandro, 5551 Linda Rosa Avenue, La Jolla, CA 92037, (US)
LEGAL REPRESENTATIVE:
Bowman, Paul Alan (28541), LLOYD WISE, TREGEAR & CO., Commonwealth House, 1-19 New Oxford Street, London WC1A 1LW, (GB)
PATENT (CC, No, Kind, Date): EP 876398 A1 981111 (Basic)
EP 876398 B1 020717
WO 9726784 970731
APPLICATION (CC, No, Date): EP 97902074 970123; WO 97US1041 970123

PRIORITY (CC, No, Date): US 10510 P 960124
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: C07K-007/08; C07K-009/00; A61K-039/00
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	200229	835
CLAIMS B	(German)	200229	828
CLAIMS B	(French)	200229	993
SPEC B	(English)	200229	18226
Total word count - document A			0
Total word count - document B			20882
Total word count - documents A + B			20882

17/3,AB/27 (Item 14 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00876227
PHARMACEUTICAL COMPOSITION COMPRISING SERUM AMYLOID P COMPONENT FOR PROPHYLACTIC OR THERAPEUTIC TREATMENT OF VIRUS INFECTIONS AND A KIT FOR DETECTING BINDING OF COMPOSITIONS TO VIRUS COMPONENTS
PHARMAZEUTISCHE ZUSAMMENSETZUNG, ENTHALTEND SERUM-AMYLOID P-KOMPONENTEN, ZUR PROPHYLAXE UND THERAPIE VON VIRALEN INFEKTIONEN SOWIE KIT ZUR DETEKTIONVON KOMPLEXEN ZWISCHEN SOLCHEN ZUSAMMENSETZUNGEN UND VIRALEN KOMPONENTEN
COMPOSITION PHARMACEUTIQUE COMPRENANT UN CONSTITUANT AMYLOIDE P DE SERUM ET DESTINEE AU TRAITEMENT PROPHYLACTIQUE OU THERAPEUTIQUE D'INFECTIONS VIRALES, ET NECESSAIRE DE DETECTION DE LA FIXATION DE COMPOSITIONS SUR DES COMPOSANTS DE VIRUS
PATENT ASSIGNEE:
Profylakse ApS, (2712590), Sobakkevej 51, 5210 Odense NV, (DK), (Proprietor designated states: all)
INVENTOR:
SVEHAG, Sven-Erik, Soebakkevej 51, 5210 Odense NV, (DK)
NIELSEN, Ellen Holm, Praestegade 12, 5300 Kerteminde, (DK)
ANDERSEN, Ove, Poul Moellersvej 26, 5230 Odense M, (DK)
LEGAL REPRESENTATIVE:
Christiansen, Ejvind (60731), Hofman-Bang Zacco A/S Hans Bekkevolds Alle 7, 2900 Hellerup, (DK)
PATENT (CC, No, Kind, Date): EP 915707 A1 990519 (Basic)
EP 915707 B1 021030
WO 97026906 970731
APPLICATION (CC, No, Date): EP 97900943 970124; WO 97DK35 970124
PRIORITY (CC, No, Date): DK 9679 960125
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: A61K-038/17; A61K-035/16; C07K-014/47; A61P-031/12
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count

CLAIMS B	(English)	200244	821
CLAIMS B	(German)	200244	814
CLAIMS B	(French)	200244	931
SPEC B	(English)	200244	6700
Total word count - document A			0
Total word count - document B			9266
Total word count - documents A + B			9266

17/3,AB/28 (Item 15 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00853195
Derivatives and analogues of 2-deoxy-2,3-didehydro-**n-acetyl neuraminic** acid and their use as antiviral agents
Derivate und analoge der 2-Deoxy-2,3-didehydro-N-acetyl-Neuraminsaure und ihre Verwendung als antivirale Agentien
Derives et analogues d'acide 2-deoxy-2,3-didehydro-N-acetyle neuraminique et leur utilisation comme agents antiviraux
PATENT ASSIGNEE:
BIOTA SCIENTIFIC MANAGEMENT PTY. LTD., (896032), (ACN 006 477 710), Level 4, 616 St Kilda Road, Melbourne, VIC 3004, (AU), (Applicant designated States: all)
INVENTOR:
von Itzstein, Laurence Mark, 118 Fulham Road, Alphington, Victoria 3078, (AU)
Wu, Wen-Yang, 34 Munro Street, Mount Waverley, Victoria 3149, (AU)
Rhan, Tho Van, Unit 4, 297 Bell Street, Coburg, Victoria 3058, (AU)
Danylec, Basil, 10 Lyndhurst Crescent, Box Hill, Victoria 3129, (AU)
Jin, Betty, 34 Munro Street, Mount Waverley, Victoria 3149, (AU)
Colman, Peter Malcolm, 74 Hotham Street, East Melbourne, Victoria 3002, (AU)
Varghese, Joseph Noozhumurry, 179 Nicholson Street, Brunswick, Victoria 3057, (AU)
LEGAL REPRESENTATIVE:
Beacham, Annabel Rose et al (89701), Frank B. Dehn & Co., European Patent Attorneys, 179 Queen Victoria Street, London EC4V 4EL, (GB)
PATENT (CC, No, Kind, Date): EP 786458 A2 970730 (Basic)
EP 786458 A3 991013
APPLICATION (CC, No, Date): EP 97100119 910424;
PRIORITY (CC, No, Date): AU 90PJ9800 900424; AU 90PK2896 901019; AU 91PK4537 910211
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LI; LU; NL; SE
RELATED PARENT NUMBER(S) - PN (AN):
EP 526543 (EP 91908682)
INTERNATIONAL PATENT CLASS: C07D-309/30; C07D-309/28; A61K-031/35

ABSTRACT EP 786458 A2
Derivatives and analogues of 2-deoxy-2,3-didehydro-**N-acetyl neuraminic** acid, pharmaceutical formulations thereof, methods for their preparation and their use in the treatment of viral infections, in particular influenza, are described.
ABSTRACT WORD COUNT: 29

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:
Available Text Language Update Word Count

CLAIMS A	(English)	9707W5	693
SPEC A	(English)	9707W5	10162
Total word count - document A			10855
Total word count - document B			0
Total word count - documents A + B			10855

17/3,AB/29 (Item 16 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00760018
PURIFIED HEPATITIS C VIRUS ENVELOPE PROTEINS FOR DIAGNOSTIC AND THERAPEUTIC USE
GEREINIGTE HEPATITIS-C-VIRUS HULLPROTEINE ZUR DIAGNOSTISCHEN UND THERAPEUTISCHEN VERWENDUNG
PROTEINES PURIFIEES D'ENVELOPPE DE VIRUS DE L'HEPATITE C A USAGE DIAGNOSTIC ET THERAPEUTIQUE
PATENT ASSIGNEE:
INNOGENETICS N.V., (713145), Industriepark Zwijnaarde 7, Box 4, 9052 Ghent, (BE), (Proprietor designated states: all)
INVENTOR:
MAERTENS, Geert, Zilversparrenstraat 64, B-8310 Brugge 3, (BE)
BOSMAN, Fons, Hulst 165, B-1745 Opwijk, (BE)
DE MARTYNOFF, Guy, Mattotstraat 71, B-1410 Waterloo, (BE)
BUYSE, Marie-Ange, E. Ronsestraat 23, B-9820 Merelbeke, (BE)
LEGAL REPRESENTATIVE:
De Clercq, Ann et al (87752), De Clercq, Brants & Partners cv., Edgard Gevaertdreef 10a, 9830 Sint-Martens-Latem, (BE)
PATENT (CC, No, Kind, Date): EP 721505 A1 960717 (Basic)
EP 721505 B1 020508
WO 9604385 960215
APPLICATION (CC, No, Date): EP 95930434 950731; WO 95EP3031 950731
PRIORITY (CC, No, Date): EP 94870132 940729
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
RELATED DIVISIONAL NUMBER(S) - PN (AN):
(EP 2002003643)
INTERNATIONAL PATENT CLASS: C12N-015/40; C07K-014/18; C07K-016/10; C12Q-001/70; G01N-033/569
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	200219	1933
CLAIMS B	(German)	200219	1676
CLAIMS B	(French)	200219	2175
SPEC B	(English)	200219	20483
Total word count - document A			0
Total word count - document B			26267
Total word count - documents A + B			26267

17/3,AB/30 (Item 17 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00744464
VIROSOME-MEDIATED INTRACELLULAR DELIVERY OF THERAPEUTIC AGENTS
INTRAZELLULARE VERABREICHUNG THERAPEUTISCHER SUSTANZENMITTELS VIROSOMEN
VIROSOMES COMME VECTEUR POUR INTRODUIRE DES AGENTS THERAPEUTIQUES A L'INTERIEUR DE CELLULES
PATENT ASSIGNEE:
INEX Pharmaceutical Corp., (1730521), 1799 West 75th Avenue, Vancouver B.C. V6P 6P2, (CA), (Proprietor designated states: all)
INVENTOR:
WILSCHUT, Jan, C., Burg Brouwerf St. 30, NL-9393 PG Garnwerd, (NL)
SCHERRER, Peter, 2664 Birch Street, Vancouver, British Columbia V6H 2T5, (CA)
CHONN, Arcadio, Suite 1702 907 Beach Avenue, Vancouver, British Columbia V6Z 1E1, (CA)
LEGAL REPRESENTATIVE:
Thul, Stephan et al (74342), Manitz, Finsterwald & Partner GbR Martin-Greif-Strasse 1, 80336 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 762870 A1 970319 (Basic)
EP 762870 B1 020911
WO 95032706 951207
APPLICATION (CC, No, Date): EP 95919296 950531; WO 95CA321 950531
PRIORITY (CC, No, Date): US 251469 940531
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: A61K-009/127; A61K-009/50; C12N-015/88
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	200237	489
CLAIMS B	(German)	200237	466
CLAIMS B	(French)	200237	571
SPEC B	(English)	200237	7847
Total word count - document A			0
Total word count - document B			9373
Total word count - documents A + B			9373

17/3,AB/31 (Item 18 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00658245
NUCLEIC ACID, EXPRESSIONVECTOR AND COMPOSITIONS FOR THE IDENTIFICATION AND SYNTHESIS OF RECOMBINANT SIALYLTRANSFERASES
NUKLEINSAURE, EXPRESSIONSVEKTOR UND ZUSAMMENSETZUNGEN ZUR IDENTIFIZIERUNG UND HERSTELLUNG VON REKOMBINANTEN SIALYLTRANSFERASEN
ACIDE NUCLEIQUE, VECTEUR D'EXPRESSION ET COMPOSITIONS POUR L'IDENTIFICATION DE SIALYLTRANSFERASES RECOMBINANTES
PATENT ASSIGNEE:
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA, (221072), 300 Lakeside Drive, 22nd Floor, Oakland, California 94612-3550, (US), (Proprietor designated states: all)
CYTEL CORPORATION, (1456331), 3525 John Hopkins Court, San Diego, CA 92121, (US), (Proprietor designated states: all)
INVENTOR:
PAULSON, James, E., 209 Torrey Pines Terrace, Del Mar, CA 90214, (US)

WEN, Xiaohong, 7260-A Carrara Place, San Diego, CA 92122, (US)
LIVINGSTON, Brian, Duane, 8615 Covina Street, San Diego, CA 92126, (US)
GILLESPIE, William, 10761 Galvin Street, Culver City, CA 90230, (US)
KELM, Sorge, Dorfstrasse 14, D-2300 Kiel 14, (DE)
BURLINGAME, Alma, L., 26 Alexander Avenue, Sausalito, CA 94965, (US)
MEDZIHRADSZKY, Katalin, 108 Burlwood Drive, San Francisco, CA 94127, (US)
LEGAL REPRESENTATIVE:
Leson, Thomas Johannes Alois, Dipl.-Ing. et al (78981), Patentanwalte Tiedtke-Buhling-Kinne & Partner, Bavariaring 4, 80336 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 632831 A1 950111 (Basic)
EP 632831 B1 021127
WO 93018157 930916
APPLICATION (CC, No, Date): EP 93907244 930309; WO 93US2002 930309
PRIORITY (CC, No, Date): US 850357 920309; US 925369 920804
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: C12N-015/54; C12N-009/10; C12N-005/10; C12N-015/85
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	200248	171
CLAIMS B	(German)	200248	149
CLAIMS B	(French)	200248	179
SPEC B	(English)	200248	18924
Total word count - document A			0
Total word count - document B			19423
Total word count - documents A + B			19423

17/3,AB/32 (Item 19 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00639902
Nucleic acid pharmaceuticals.
Nukleinsaure als pharmazeutische Zubereitungen.
Acides nucleiques comme produits pharmaceutiques.
PATENT ASSIGNEE:
MERCK & CO. INC., (200479), 126, East Lincoln Avenue P.O. Box 2000, Rahway New Jersey 07065-0900, (US), (applicant designated states: AT;BE;CH;DE;DK;ES;FR;GB;GR;IE;IT;LI;LU;NL;PT;SE)
VICAL INCORPORATED, (1762940), 9373 Towne Centre Drive, Suite 100, San Diego, California 92121, (US), (applicant designated states: AT;BE;CH;DE;DK;ES;FR;GB;GR;IE;IT;LI;LU;NL;PT;SE)
INVENTOR:
Donnelly, John J., 1505 Bierwood Road, Havertown, PA 19083, (US)
Montgomery, Donna L, 9, Hickory Lane, Chalfont , PA 18914, (US)
Dwarki, Varavani J., 1175 Broadway Apt. N, Alameda, CA 94501, (US)
Parker, Suezanne E., 3646 Carmel Landing, San Diego, CA 92130, (US)
Liu, Magaret A., 4 Cushman Road, Rosemont, PA 19190, (US)
Shiver, John W., 125 Beulah Road, Doylestown, PA 18901, (US)
Ulmer, Jeffrey B., 128 Dolly Circle, Chalfont, PA 18914, (US)
LEGAL REPRESENTATIVE:
Cole, William Gwyn et al (29438), European Patent Department Merck & Co., Inc. Terlings Park Eastwick Road, Harlow Essex CM20 2QR, (GB)

PATENT (CC, No, Kind, Date): EP 620277 A1 941019 (Basic)
APPLICATION (CC, No, Date): EP 94200605 940309;
PRIORITY (CC, No, Date): US 32383 930318; US 89985 930708
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; NL; PT; SE
INTERNATIONAL PATENT CLASS: C12N-015/44; A61K-048/00; A61K-031/70;
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	EPABF2	1579
SPEC A	(English)	EPABF2	20851
Total word count - document A			22430
Total word count - document B			0
Total word count - documents A + B			22430

17/3,AB/33 (Item 20 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00620345
ANTI-INFLAMMATORY TOLEROGENIC AND IMMUNOINHIBITING PROPERTIES OF CARBOHYDRATE BINDING-PEPTIDES
ENTZUNDUNGSHEMMENDE TOLEROGENE UND IMMUNOINHIBITORISCHE EIGENSCHAFTEN VON KARBOHYDRATE BINDENDE PEPTIDE
PROPRIETES ANTI-INFLAMMATOIRES, TOLEROGENES ET IMMUNO-INHIBITRICES DE PEPTIDES DE FIXATION D'HYDRATE DE GLUCIDE
PATENT ASSIGNEE:
ALBERTA RESEARCH COUNCIL, (1070134), 250 Karl Clark Road, Edmonton Alberta T6H 5X2, (CA), (Proprietor designated states: all)
INVENTOR:
HEERZE, Louis, D., 10, 10811 86 Avenue, Edmonton, Alberta T6E 2N1, (CA)
ARMSTRONG, Glen, D., 7951 91 Avenue, Edmonton, Alberta T6C 1P9, (CA)
SMITH, Richard, 1010 Buchanan Place, Edmonton, Alberta T6R 2A6, (CA)
LEGAL REPRESENTATIVE:
Nash, David Allan et al (59251), Haseltine Lake & Co., Imperial House, 15-19 Kingsway, London WC2B 6UD, (GB)
PATENT (CC, No, Kind, Date): EP 666758 A1 950816 (Basic)
EP 666758 B1 011212
WO 9407517 940414
APPLICATION (CC, No, Date): EP 93921770 931004; WO 93CA415 931004
PRIORITY (CC, No, Date): US 956043 921002; US 995503 921221
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: A61K-038/02
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	200150	1357
CLAIMS B	(German)	200150	1226
CLAIMS B	(French)	200150	1502
SPEC B	(English)	200150	14409
Total word count - document A			0
Total word count - document B			18494
Total word count - documents A + B			18494

17/3,AB/34 (Item 21 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00619659
RECOMBINANT VIRUSES DISPLAYING A NONVIRAL POLYPEPTIDE ON THEIR EXTERNAL SURFACE
REKOMBINANTE VIREN, DIE AN IHRER AUSSEREN OBERFLACHE EIN NICHTVIRALES POLYPEPTID PRASENTIEREN
VIRUS RECOMBINES PRESENTANT UN POLYPEPTIDE NON-VIRAL SUR LEUR SURFACE EXTERNE
PATENT ASSIGNEE:
Biofocus Discovery Limited, (3098434), Cambridge Science Park, Milton Road, Cambridge CB4 4FD, (GB), (Proprietor designated states: all)
INVENTOR:
RUSSELL, Stephen James 10 Courtyards, Little Shelford, Cambridgeshire CB2 5ER, (GB)
HAWKINS, Robert Edward, 6 The Lawns, Cambridge CB3 0RU, (GB)
WINTER, Gregory Paul, Trinity Hall, Trinity Lane, Cambridge CB2 1TJ, (GB)
LEGAL REPRESENTATIVE:
Matthews, Heather Clare et al (46391), Keith W Nash & Co Pearl Assurance House 90-92 Regent Street, Cambridge CB2 1DP, (GB)
PATENT (CC, No, Kind, Date): EP 670905 A1 950913 (Basic)
EP 670905 B1 030723
WO 94006920 940331
APPLICATION (CC, No, Date): EP 93920989 930922; WO 93GB1992 930922
PRIORITY (CC, No, Date): GB 9220010 920922; GB 9304962 930311
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LI; LU; MC; NL; PT; SE
INTERNATIONAL PATENT CLASS: C12N-015/86; A61K-048/00; C12N-015/10; C12N-015/87; C12N-015/62
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	200330	569
CLAIMS B	(German)	200330	580
CLAIMS B	(French)	200330	620
SPEC B	(English)	200330	18000
Total word count - document A			0
Total word count - document B			19769
Total word count - documents A + B			19769

17/3,AB/35 (Item 22 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00556227
LIVER ENRICHED TRANSCRIPTION FACTOR
AUS LEBER ANGEREICHERTER TRANSKRIPTIONSFAKTOR
FACTEUR DE TRANSCRIPTION ENRICHI PAR EXTRAITS HEPATIQUES
PATENT ASSIGNEE:
THE ROCKEFELLER UNIVERSITY, (315600), 1230 York Avenue, New York, NY 10021, (US), (Proprietor designated states: all)
INVENTOR:

SLADEK, Frances, M., 500 East 63rd Street, Apt. 10D, New York, NY 10021, (US)
ZHONG, Weimin, 1230 York Avenue, New York, NY 10021, (US)
DARNELL, James, E., Jr., 96 Edgewood Avenue, Larchmont, NY 10538, (US)
LEGAL REPRESENTATIVE:
Mercer, Christopher Paul (46611), Carpmaels & Ransford 43, Bloomsbury Square, London WC1A 2RA, (GB)
PATENT (CC, No, Kind, Date): EP 564592 A1 931013 (Basic)
EP 564592 B1 991013
WO 9211365 920709
APPLICATION (CC, No, Date): EP 92903912 911223; WO 91US9733 911223
PRIORITY (CC, No, Date): US 631720 901221
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LI; LU; NL; SE
INTERNATIONAL PATENT CLASS: C12N-015/12; C12N-001/21; C12N-001/19; C12N-015/67; C12N-005/10; C12P-021/08; C12N-015/62; C12N-015/11; C12N-009/00; C07K-014/00; C07K-002/00
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	9941	1087
CLAIMS B	(German)	9941	1069
CLAIMS B	(French)	9941	1236
SPEC B	(English)	9941	16277
Total word count - document A			0
Total word count - document B			19669
Total word count - documents A + B			19669

17/3,AB/36 (Item 23 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00538915
Proteinaceous lipid-containing particles.
Fett enthaltende proteinhaltige Partikel.
Particules proteico-lipidiques.
PATENT ASSIGNEE:
BRITISH BIO-TECHNOLOGY LIMITED, (970611), Watlington Road, Cowley Oxford OX4 5LY, (GB), (applicant designated states: AT;BE;CH;DE;DK;ES;FR;GB;GR;IT;LI;LU;NL;PT;SE)
INVENTOR:
Adams, Sally Elizabeth, British Bio-technology Limited, Watlington Road, Cowley, Oxford OX4 5LY, (GB)
Burns, Nigel Robert, British Bio-technology Limited, Watlington Road, Cowley, Oxford OX4 5LY, (GB)
French, Timothy John, British Bio-technology Limited, Watlington Road, Cowley, Oxford OX4 5LY, (GB)
Gearing, Andrew John Hubert, British Bio-technology Limited, Watlington Road, Cowley, Oxford OX4 5LY, (GB)
Kingsman, Alan John, British Bio-technology Limited, Watlington Road, Cowley, Oxford OX4 5LY, (GB)
Kingsman, Susan Mary, British Bio-technology Limited, Watlington Road, Cowley, Oxford OX4 5LY, (GB)
LEGAL REPRESENTATIVE:
Sheard, Andrew Gregory et al (50962), Kilburn & Strode 30, John Street, London WC1N 2DD, (GB)

PATENT (CC, No, Kind, Date): EP 508809 A1 921014 (Basic)
APPLICATION (CC, No, Date): EP 92303223 920410;
PRIORITY (CC, No, Date): GB 9107631 910410
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LI; LU; NL; PT; SE
INTERNATIONAL PATENT CLASS: C12N-007/04; C12N-015/86; C12N-015/12; C12N-015/41; C12N-015/47; C12N-015/49; C12N-015/87; C12N-005/10; C12N-015/85; A61K-037/00;

ABSTRACT EP 508809 A1
Proteinaceous, lipid-containing particles can be prepared by co-expressing in a host cell (i) a self-assembling protein moiety in circumstances where the protein assembles to form a core, which then buds off from the host cell, thereby acquiring a lipid envelope derived from the host cell membrane and (ii) a membrane-bound protein moiety, which becomes integrated in the lipid envelope. The particles have a wide variety of uses. They may be used as an antigen presentation system, or they may for example have site-specific targeting ability, fusogenic properties, enzymic activity, cytotoxic activity, diagnostic utility and/or pharmaceutical activity. (see image in original document)
ABSTRACT WORD COUNT: 103

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	EPABF1	944
SPEC A	(English)	EPABF1	12261
Total word count - document A			13205
Total word count - document B			0
Total word count - documents A + B			13205

17/3,AB/37 (Item 24 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00531795
alpha 2-3 Sialyltransferase
Alpha-2-3-Sialyltransferase
Alpha 2-3 Sialyltransferase
PATENT ASSIGNEE:
KYOWA HAKKO KOGYO CO., LTD., (229062), 6-1, Ohtemachi 1-chome, Chiyoda-ku, Tokyo-to, (JP), (applicant designated states: DE;FR;GB;IT)
INVENTOR:
Sasaki, Katsutoshi, 3-6-6, Asahimachi, Machida-shi, Tokyo-to, (JP)
Watanabe, Etsuyo, 1458-28, Okagami, Asao-ku, Kawasaki-shi, Kanagawa-ken, (JP)
Nishi, Tatsunari, 3-9-13, Nakamachi, Machida-shi, Tokyo, (JP)
Sekine, Susumu, 2-20-10, Higashifuchinobe, Sagamihara-shi, Kanagawa-ken, (JP)
Hanai, Nobuo, 3-3-3, Fujimi, Sagamihara-shi, Kanagawa-ken, (JP)
Hasegawa, Mamoru, 1-9-26, Katahira, Asao-ku, Kawasaki-shi, Kanagawa-ken, (JP)
LEGAL REPRESENTATIVE:
VOSSIUS & PARTNER (100311), Postfach 86 07 67, 81634 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 552470 A1 930728 (Basic)
EP 552470 B1 980311
APPLICATION (CC, No, Date): EP 92121482 921217;

PRIORITY (CC, No, Date): JP 91333661 911217; JP 9291044 920410
DESIGNATED STATES: DE; FR; GB; IT
INTERNATIONAL PATENT CLASS: C12N-015/54; C12N-009/10; C12Q-001/68; C12P-021/00; C12N-001/21; C12N-001/21; C12R-001/19

ABSTRACT EP 552470 A1
There are provided a novel a2->3 sialyltransferase expressed by a cloned gene from human cells, a cDNA encoding the a2->3 sialyltransferase, a method for detecting or suppressing the expression of an a2->3 sialyltransferase by use of said cDNA, a recombinant vector containing said cDNA, a cell containing said vector, and their production processes.
ABSTRACT WORD COUNT: 55

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	9811	660
CLAIMS B	(German)	9811	634
CLAIMS B	(French)	9811	768
SPEC B	(English)	9811	21445
Total word count - document A			0
Total word count - document B			23507
Total word count - documents A + B			23507

17/3,AB/38 (Item 25 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00502066
AN IgG-1 HUMAN MONOCLONAL ANTIBODY REACTIVE WITH AN HIV-1 GLYCOPROTEIN AND METHOD OF USE
EIN MIT HIV-1-GLYKOPROTEIN REAGIERENDER MENSCHLICHER MONOKLONALER IgG-1-ANTIKORPER UND VERWENDUNGSMETHODE
ANTICORPS MONOCLONAL HUMAIN D'IgG-1 REAGISSANT AVEC UNE GLYCOPROTEINE DE HIV-1 ET PROCEDE D'UTILISATION
PATENT ASSIGNEE:
ROGER WILLIAMS GENERAL HOSPITAL, (1118100), 825 Chalkstone Avenue, Providence Rhode Island 02908, (US), (Proprietor designated states: all)
INVENTOR:
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PATENT (CC, No, Kind, Date): EP 517815 A1 921216 (Basic)
EP 517815 A1 930922
EP 517815 B1 991006
WO 9113148 910905
APPLICATION (CC, No, Date): EP 91905752 910226; WO 91US1394 910226
PRIORITY (CC, No, Date): US 485179 900226
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LI; LU; NL; SE
INTERNATIONAL PATENT CLASS: C07K-016/10; C12N-005/28; C12N-015/13; C12P-021/08; A61K-039/395; G01N-033/577
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English

FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	9940	567
CLAIMS B	(German)	9940	610
CLAIMS B	(French)	9940	637
SPEC B	(English)	9940	10655
Total word count - document A			0
Total word count - document B			12469
Total word count - documents A + B			12469

17/3,AB/39 (Item 26 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00446350
MOLECULAR CLONING OF GENOMIC AND cDNA SEQUENCES ENCODING CELLULAR RECEPTORS FOR POLIOVIRUS
MOLEKULARES KLONIEREN VON GENOMISCHEN UND CDNA-SEQUENZEN, DIE FUR ZELLULARE REZEPTOREN FUR POLIOVIRUS KODIEREN
CLONAGE MOLECULAIRE DE SEQUENCES GENOMIQUES ET D'ADN COMPLEMENTAIRE CODANT DES RECEPTEURS CELLULAIRES DU VIRUS POLIOMYELITIQUE
PATENT ASSIGNEE:
THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK, (477541), West 116th Street and Broadway, New York, New York 10027, (US), (Proprietor designated states: all)
INVENTOR:
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MENDELSOHN, Cathy, 3, rue Kageneck, F-67000 Strasbourg, (FR)
COSTANTINI, Frank 1611 York Avenue, Apartment 4-J New York,, NY 10021, (US)
LEGAL REPRESENTATIVE:
Lawrence, John et al (60371), Barker Brettell 138 Hagley Road Edgbaston, Birmingham B16 9PW, (GB)
PATENT (CC, No, Kind, Date): EP 462215 A1 911227 (Basic)
EP 462215 A1 920923
EP 462215 B1 020619
WO 9010699 900920
APPLICATION (CC, No, Date): EP 90905140 900309; WO 90US1320 900309
PRIORITY (CC, No, Date): US 321957 890310
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; IT; LI; LU; NL; SE
INTERNATIONAL PATENT CLASS: C12N-015/12; C12N-001/11; C12P-021/02; C07K-014/00; C07K-004/02
NOTE:
No A-document published by EPO
LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	200225	396
CLAIMS B	(German)	200225	370
CLAIMS B	(French)	200225	461
SPEC B	(English)	200225	9978
Total word count - document A			0
Total word count - document B			11205
Total word count - documents A + B			11205

Devi, S.
10/081170

-key terms

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     FILE 'REGISTRY' ENTERED AT 14:35:51 ON 18 DEC 2003
                E SIALIC ACID/CN 5
                E "N-ACETYLNEURAMINIC ACID"/CN 5
L1             1 S E3
                E "N-GLYCOLYLNEURAMINIC ACID"/CN 5
L2             1 S E3

L3             2 S L1 OR L2

     FILE 'HCAPLUS' ENTERED AT 14:36:35 ON 18 DEC 2003
L1             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "N-ACETYLNEURAMINIC
                  ACID"/CN
L2             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "N-GLYCOLYLNEURAMINIC
                  ACID"/CN
L3             2 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 OR L2
L4         22557 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 OR SIALIC OR
                  N(W)(ACETYLNEURAMINIC OR GLYCOLYLNEURAMINIC OR (ACETYL
                  OR AC OR GLYCOLYL)(W)(NEU OR NEURAMINIC)) OR NEUNAC OR
                  NEUGC
L5          8360 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 AND CELL
L6          1426 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 AND (MAMMAL? OR
                  SWINE OR PIG OR PIGLET OR HOG OR BOVINE OR OX OR COW OR
                  CATTLE OR OX OR OXEN OR MONKEY OR SIMIAN OR APE OR CHIMP
                  OR CHIMPANZ? OR CANINE OR DOG OR MDCK? OR MADIN DARBY OR
                  MINK OR AVIAN OR BIRD)
L7           101 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 AND (MUTANT OR
                  MUTAGEN? OR POLYMORPH? OR POLY MORPH?)
L8            15 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L7 AND INFLUENZ?

L8   ANSWER 1 OF 15  HCAPLUS  COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER:        2002:907161  HCAPLUS
DOCUMENT NUMBER:         138:13500
TITLE:                   Superantigen-glycolipid conjugates loaded onto
                         antigen presening cells for adoptive
                         immunotherapy of neoplastic and infectious
                         diseases
INVENTOR(S):             Terman, David S.
PATENT ASSIGNEE(S):      USA
SOURCE:                  U.S. Pat. Appl. Publ., 167 pp.
                         CODEN: USXXCO
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.   DATE
     ----------------  ----  --------      ---------------   --------
     US 2002177551      A1   20021128      US 2001-870759    20010530
PRIORITY APPLN. INFO.:                    US 2000-208128P  P 20000531
AB   The present invention comprises compns. and methods for treating a
     tumor or neoplastic disease in a host, The methods employ conjugates
     comprising superantigen polypeptides, nucleic acids with other
     structures that preferentially bind to tumor cells and are
     capable of inducing apoptosis.  Also provided are
     superantigen-glycolipid conjugates and vesicles that are loaded onto
     antigen presenting cells to activate both T cells
     and NKT cells.  Cell-based vaccines comprise
     tumor cells engineered to express a superantigen along
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with glycolipids products which, when expressed, render the **cells** capable of eliciting an effective anti-tumor immune response in a **mammal** into which these **cells** are introduced. Included among these compns. are tumor **cells**, hybrid **cells** of tumor **cells** and accessory **cells**, preferably dendritic **cells**. Also provided are tumoricidal T **cells** and NKT **cells** devoid of inhibitory receptors or inhibitory signaling motifs which are hyperresponsive to the the above compns. and lipid-based tumor associated antigens that can be administered for adoptive immunotherapy of cancer and infectious diseases.

L8 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:676181 HCAPLUS
DOCUMENT NUMBER: 137:214224
TITLE: Identification of lectin-resistant animal **cells** with reduced **sialic** acid for **influenza** virus **mutant** capable of replicating in an altered host **cell**
INVENTOR(S): Kawaoka, Yoshihiro
PATENT ASSIGNEE(S): Wisconsin Alumni Research Foundation, USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002068632	A2	20020906	WO 2002-US5455	20020222
WO 2002068632	A3	20030530		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002197705	A1	20021226	US 2002-81170	20020222
EP 1364006	A2	20031126	EP 2002-724994	20020222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2001-271044P P 20010223
WO 2002-US5455 W 20020222

AB The invention provides an isolated **mutant** vertebrate **cell** which has altered expression of **sialic** acid for **influenza** virus, and methods of preparing and using the **mutant cell**. The invention provides **cells** useful to propagate **influenza** virus **mutants** having reduced sialidase activity caused by deletion mutation in NA gene. To produce **cell** lines with a decreased level of **sialic** acid expression on the **cell** surface, two

lectins were used, SNA and MAA, to treat the **cells**. The **MDCK cell** line, which supports the growth of **influenza** viruses, was used as a parent **cell** for lectin selection. Viruses lacking sialidase activity can grow efficiently in **cells** expressing a reduced level of **sialic** acid because the viral glycoproteins are not sialylated extensively compared with those in normal **cell** lines and are not bound by the HA (hemagglutinin), thus preventing viral aggregation.

IT **131-48-6, N-Acetylneuraminic** acid
1113-83-3, N-Glycolylneuraminic acid
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(identification of lectin-resistant animal **cells** with reduced **sialic** acid for **influenza** virus **mutant** capable of replicating in an altered host **cell**)

L8 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:151302 HCAPLUS
DOCUMENT NUMBER: 137:17659
TITLE: Use of pseudotyped retroviral vectors to analyze the receptor-binding pocket of hemagglutinin from a pathogenic **avian influenza** A virus (H7 subtype)
AUTHOR(S): Lin, Amy H.; Cannon, Paula M.
CORPORATE SOURCE: Gene Therapy Laboratories, Norris Cancer Center, University of Southern California Keck School of Medicine, Los Angeles, CA, 90033, USA
SOURCE: Virus Research (2002), 83(1-2), 43-56
CODEN: VIREDF; ISSN: 0168-1702
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The hemagglutinin (HA) protein of **influenza** virus binds to terminal **sialic** acid residues present on **cell** surface glycoproteins and glycolipids. The specific amino acids involved in this interaction have been identified for a H3 subtype HA from the human non-pathogenic virus, A/Aichi/2/68, by both crystallog. and **mutagenesis** studies. We were interested to examine the receptor-binding pocket of a H7 subtype protein from the **avian** pathogenic virus A/FPV/Rostock/34. Accordingly, we made amino acid substitutions at 6 conserved residues (Y88, T126, H174, E181, L185, and G219), suggested by comparison with the receptor-binding pocket of the H3 protein, and analyzed the resulting proteins using pseudotyped retroviral vectors. The use of these vectors enabled us to quantitate both the ability of the **mutant** HA proteins to bind with receptor-expressing **cells**, and also to promote virus-**cell** fusion by measuring vector titer. Using this system, we identified a subset of **mutants** with impaired receptor-binding activity and a corresponding decrease in titer, but which retained the ability to induce syncytia in low pH **cell-cell** fusion assays. The most severely affected **mutants** contained >1 substitution, with the triple **mutant** Y88F/E181Q/G219K being the most defective. These observations highlight the importance of multiple contact points for the interaction between **sialic** acid and HA.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE

FOR THIS RECORD. ALL CITATIONS AVAILABLE
IN THE RE FORMAT

L8 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:544052 HCAPLUS
DOCUMENT NUMBER: 134:250464
TITLE: **Influenza** virus infection of desialylated **cells**
AUTHOR(S): Stray, Stephen J.; Cummings, Richard D.; Air, Gillian M.
CORPORATE SOURCE: Department of Biochemistry & Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, 73190, USA
SOURCE: Glycobiology (2000), 10(7), 649-658
CODEN: GLYCE3; ISSN: 0959-6658
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Sialic** acid has long been considered to be the sole receptor for **influenza** virus. The viral hemagglutinin (HA) is known to bind **cell** surface **sialic** acid, and **sialic** acids on viral glycoproteins are cleaved by the viral neuraminidase (NA) to promote efficient release of progeny virus particles. However, NWS-Mvi, a **mutant** virus completely lacking NA, grows well in **MDCK cells** continuously treated with exogenous neuraminidase (sialidase). Exogenous sialidase quant. releases all **sialic** acids from purified glycoproteins and glycolipids of **MDCK cells** and efficiently removes surface **sialic** acid from intact **cells**. Binding of NWS-Mvi and parent **influenza** viruses to **MDCK cells** is indistinguishable, and is only partially reduced by sialidase treatment of the **cells**. Both **mutant** and wild-type viruses enter enzymically desialylated **cells** and initiate transcription. The ability of **influenza** A reassortant viruses to infect desialylated **cells** is shared by recent H3N2 clin. isolates, suggesting that this may be a general property of **influenza** A viruses. We propose that **influenza** virus infection can result from **sialic** acid-independent receptors, either directly or in a multistage process. When **sialic** acid is present, it may act to enhance virus binding to the **cell** surface to increase interaction with secondary receptors to mediate entry. Understanding virus entry will be critical to further efforts in infection control and prevention.
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:215573 HCAPLUS
DOCUMENT NUMBER: 130:247830
TITLE: Lipid-containing vectors with **sialic** acid-nonbinding but fusogenic **influenza** A virus hemagglutinin **mutant** for use in targeted bioactive substance delivery
INVENTOR(S): Bates, Paul; Mir-Shekari, Yasamin
PATENT ASSIGNEE(S): The Trustees of the University of Pennsylvania,

	USA
SOURCE:	PCT Int. Appl., 58 pp.
	CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9913905	A1	19990325	WO 1998-US19552	19980917
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9893994	A1	19990405	AU 1998-93994	19980917
US 6416997	B1	20020709	US 2000-525392	20000315

PRIORITY APPLN. INFO.:	US 1997-59239P	P	19970918
	WO 1998-US19552	W	19980917

AB The invention relates to a lipid containing vector capable of fusing to a **cell** membrane and delivering a compound contained therein to a **cell**, and methods of use thereof. The vector contains an **influenza** A virus hemagglutinin mutated such that it no longer binds to its normal **sialic** acid receptor but retains its fusogenic capability. The vector may contain another targeting mol., e.g., a pseudotyped murine leukemia virus. Such a virus, expressing T155S,L226V-hemagglutinin in its envelope, and a chimeric Tva-EGF protein was able to fuse with A431 **cells** expressing the EGF receptor.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER:	1998:523247 HCAPLUS
DOCUMENT NUMBER:	129:228033
TITLE:	Differences in the biological phenotype of low-yielding (L) and high-yielding (H) variants of **swine influenza** virus A/NJ/11/76 are associated with their different receptor-binding activity
AUTHOR(S):	Gambaryan, A. S.; Matrosovich, M. N.; Bender, C. A.; Kilbourne, E. D.
CORPORATE SOURCE:	M. P. Chumakov Institute of Poliomyelitis and Viral Encephalitides, Russian Academy of Medical Sciences, Moscow, 142782, Russia
SOURCE:	Virology (1998), 247(2), 223-231
	CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER:	Academic Press
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Low- (L) and high-yielding (H) variants of A/sw/NJ/11/76 **influenza** virus were compared for their growth properties in embryonated chicken eggs and **MDCK cells** and for their binding affinity for the membrane fractions prepared from **cells** of the chicken embryo allantoic membrane, **MDCK** , and **swine** tracheal **cells**, as well as for soluble **sialic** acid containing macromols. and monovalent sialosides. The authors have shown that during infection in **MDCK**

cells and in eggs, the progeny of the L variant remain predominantly **cell** associated, in contrast to those of H. As a result, accumulation of the L **mutant** in allantoic or culture fluid is significantly slowed in comparison with the H variant. Visualization of the infectious foci formed by the viruses in **MDCK cell** monolayers and on the allantoic membrane revealed that L spreads predominantly from **cell** to **cell**, while the spread of H involves release of the virus progeny into solution and its rapid distribution over the **cell** monolayer via convectional flow of the liquid In the binding assays, L displayed significantly higher binding affinity than H for cellular membranes, gangliosides, and sialylglycoproteins, however, the affinity of the variants for the monovalent **sialic** acid compds. was comparable. Unlike H, L bound strongly to dextran sulfate. The data obtained suggest that all distinctions of the L and H biol. phenotypes reported previously could be rationally explained by a more avid binding of the L variant to the surface of target **cells**, and that this effect is mainly due to enhanced electrostatic interactions. (c) 1998 Academic Press.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:255530 HCAPLUS
DOCUMENT NUMBER: 129:183
TITLE: Generation and characterization of a **mutant** of **influenza** A virus selected with the neuraminidase inhibitor BCX-140
AUTHOR(S): Bantia, Shanta; Ghate, Anita A.; Ananth, Sandya L.; Babu, Sudhakar Y.; Air, Gillian M.; Walsh, Gerald M.
CORPORATE SOURCE: BioCryst Pharmaceuticals, Inc., Birmingham, AL, 35244, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1998), 42(4), 801-807
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Influenza** neuraminidase (NA) plays an important role in viral replication, and characterization of viruses resistant to NA inhibitors will help elucidate the role of active-site residues. This information will assist in designing better inhibitors targeted to essential active-site residues that cannot generate drug-resistant mutations. In the present study we used the benzoic acid-based inhibitor BCX-140 to select and characterize resistant viruses. BCX-140 binds to the NA active site in an orientation that is opposite that of a **sialic** acid-based compound, 4-guanidino-2,4-dideoxy-2,3-dehydro-**N**-**acetylneuraminic** acid (GANA). Thus, the guanidino group of BCX-140 binds to Glu-276, whereas in GANA the guanidino group binds to Glu-119. We passaged **influenza** A/Singapore/1/57 (H2N2) in **Madin-Darby canine** kidney **cells** in the presence of BCX-140, and virus resistant to this inhibitor was selected after six passages. The NA of this

mutant was still sensitive to inhibition by BCX-140. However, the **mutant** virus was resistant to BCX-140 in plaque and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays. Sequence anal. of hemagglutinin (HA) and NA genes revealed changes in both, although none were in the active site of the NA. Depending on the method of selection of the resistant virus, two types of changes associated with the **sialic** acid binding site were seen in the HA. One is a change in HA1 of Ala-133 to Thr, a residue close to the binding site, while the other change was Arg-132 of HA1 to Gln, which in HA1 of serotype H3 is a **sialic** acid contact (Asn-137). Binding studies revealed that both types of resistant viruses had reduced receptor binding affinity compared to that of the wild type. Thus, resistance to BCX-140 was generated by modifying the HA. NA active-site residue 276 may be essential for activity, and thus, it cannot be changed to generate resistance. However, drug-induced changes in the HA can result in a virus that is less dependent on NA activity for growth in **cells** and, hence, resistant to NA inhibitors.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:78340 HCAPLUS
DOCUMENT NUMBER: 128:190899
TITLE: Studies of the binding properties of **influenza** hemagglutinin receptor-site **mutants**
AUTHOR(S): Martin, Javier; Wharton, Stephen A.; Lin, Yi Pu; Takemoto, Darin K.; Skehel, John J.; Wiley, Don C.; Steinhauer, David A.
CORPORATE SOURCE: Division of Virology, National Institute for Medical Research, The Ridgeway, London, NW7 1AA, UK
SOURCE: Virology (1998), 241(1), 101-111
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Site-specific mutations have been made in the **influenza** hemagglutinin (HA) receptor binding site to assess the contribution of individual amino acid residues to receptor recognition. Screening of **mutant** HAs, expressed using recombinant vaccinia virus-infected **cells**, for their abilities to bind human erythrocytes indicated that substitutions involving conserved residues Y98F, H183F, and L194A severely restricted binding and that the substitution W153A prevented **cell** surface expression of HA. Mutation of residues E190 and S228 that are in positions to form hydrogen bonds with the 9-OH of **sialic** acid appeared to increase erythrocyte binding slightly, as did the substitution G225R. Substitutions of other residues that are directly or indirectly involved in receptor binding, S136T, S136A, Y195F, G225D, and L226P, had intermediate effects on binding between these two extremes. Ests. of changes in receptor binding specificity based on inhibition of binding to erythrocytes by nonimmune horse sera indicated that **mutants** G225R and L226P, unlike wild-type HA, were not inhibited; Y195F and G225D **mutants** were, like

wild type, inhibited; and erythrocyte binding by **mutants** S136A, S136T, E190A, and S228G was only partially inhibited. Viruses containing **mutant** HAs Y98F, S136T, G225D, and S228G that cover the range of erythrocyte binding properties observed were also constructed by transfection. All four transfectant viruses replicated in **MDCK cells** and embryonated hens' eggs as efficiently as wild-type X-31 virus, although the Y98F **mutant** virus was unable to agglutinate erythrocytes. **Mutant MDCK cells** that have reduced levels of **cell** surface **sialic** acids were susceptible to infection by S136T, G225D, and S228G transfectant viruses and by wild type but not by the Y98F transfectant virus.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:251363 HCAPLUS
DOCUMENT NUMBER: 126:311796
TITLE: Catalytic and framework mutations in the neuraminidase active site of **influenza** viruses that are resistant to 4-guanidino-Neu5Ac2en
AUTHOR(S): Gubareva, Larisa V.; Robinson, Matthew J.; Bethell, Richard C.; Webster, Robert G.
CORPORATE SOURCE: Dep. Virology/Molecular Biol., St. Jude Children's Res. Hospital, Memphis, TN, 38101, USA
SOURCE: Journal of Virology (1997), 71(5), 3385-3390
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Here we report the isolation of **influenza** virus A/turkey/Minnesota/833/80 (H4N2) with a mutation at the catalytic residue of the neuraminidase (NA) active site, rendering it resistant to the novel NA inhibitor 4-guanidino-Neu5Ac2en (GG167). The resistance of the **mutant** stems from replacement of one of three invariant arginines (Arg292→Lys) that are conserved among all viral and bacterial NAs and participate in the conformational change of **sialic** acid moiety necessary for substrate catalysis. The Lys292 **mutant** was selected in vitro after 15 passages at increasing concns. of GG167 (from 0.1 to 1,000 μM), conditions that earlier gave rise to GG167-resistant **mutants** with a substitution at the framework residue Glu119. Both types of **mutants** showed similar degrees of resistance in plaque reduction assays, but the Lys292 **mutant** was more sensitive to the inhibitor in NA inhibition tests that were **mutants** bearing a substitution at framework residue 119 (Asp, Ala, or Gly). Cross-resistance to other NA inhibitors (4-amino-Neu5Ac2en and Neu5Ac2en) varied among **mutants** resistant to GG167, being lowest for Lys292 and highest for Asp119. All GG167-resistant **mutants** demonstrated markedly reduced NA activity, only 3 to 50% of the parental level, depending on the particular amino acid substitution. The catalytic **mutant** (Lys292) showed a significant change in pH optimum of NA activity, from 5.9 to 5.3. All of the **mutant** NAs were less stable than the parental enzyme at low pH. Despite their impaired NA

activity, the GG167-resistant **mutants** grew as well as parental virus in **Madin-Darby canine** kidney **cells** or in embryonated chicken eggs. However, the infectivity in mice was 500-fold lower for Lys292 than for the parental virus. These findings demonstrate that amino acid substitution in the NA active site at the catalytic or framework residues, followed by multiple passages in vitro, in the presence of increasing concns. of the NA inhibitor GG167, generates GG167-resistant viruses with reduced NA activity and decreased infectivity in animals.

L8 ANSWER 10 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:99272 HCAPLUS
DOCUMENT NUMBER: 124:140772
TITLE: Characterization of **mutants** of **influenza** A virus selected with the neuraminidase inhibitor 4-guanidino-Neu5Ac2en
AUTHOR(S): Gubareva, L. V.; Bethell, R.; Hart, G. J.; Murti, K. G.; Penn, C. R.; Webster, R. G.
CORPORATE SOURCE: Dep. Virology/Molecular Biology, St. Jude Children's Res. Hospital, Memphis, TN, 38101, USA
SOURCE: Journal of Virology (1996), 70(3), 1818-27
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The development of resistance to the title neuraminidase inhibitor, 4-guanidino-2,4-dideoxy-2,3-dehydro-**N-acetylneuraminic** acid (I), in **influenza** viruses was studied by serial passage of A/Turkey/Minnesota/833/80 (H4N2) in **Madin-Darby canine** kidney **cells** in the presence of increasing concns. of I. Resistant **mutants**, selected after 8 passages, had a 10,000-fold reduction in sensitivity to I in plaque assays, but their affinity (1/Kd) to I was similar to that of the parental virus. Electron microscopic anal. revealed aggregation of the **mutant** virus at the **cell** surface in the presence of I. Sequence anal. established that a substitution had occurred in the neuraminidase (Arg-249 to Lys) and in the HA2 subunit of the hemagglutinin (Gly-75 to Glu), in the vicinity of the proposed 2nd **sialic** acid binding site. The change at residue 249 appears to be a chance mutation, for this **mutant** could not be reisolated, whereas subsequent expts. indicate changes in the hemagglutinin. After 13 passages of the parental virus, **mutants** that were resistant to the high concns. of inhibitor tested were obtained. These viruses retained their drug-resistant phenotype even after 5 passages without I. Electron microscopic anal. revealed no aggregation of virus on the surface of infected **cells** in the presence of I. Sequence anal. of the neuraminidase gene from these drug-resistant **mutants** revealed an addnl. substitution of Glu to Ala at the conserved amino acid residue 119. This substitution is responsible for reducing the affinity of I to the neuraminidase. These findings suggest that the emergence of **mutants** resistant to I is a multistep process requiring prolonged exposure to I.

L8 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1993:445036 HCAPLUS
DOCUMENT NUMBER: 119:45036
TITLE: A single point mutation of the **influenza** C virus glycoprotein (HEF) changes the viral receptor-binding activity
AUTHOR(S): Szepanski, Sigrun; Gross, H. J.; Brossmer, R.; Klenk, H. D.; Herrler, G.
CORPORATE SOURCE: Inst. Virol., Phillips-Univ., Marburg, Germany
SOURCE: Virology (1992), 188(1), 85-92
CODEN: VIRLAX; ISSN: 0042-6822
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A **mutant** was derived with a change in the **cell** tropism from strain JHB/1/66 of **influenza** C virus. The **mutant** was able to grow in a subline of **Madin-Darby canine** kidney **cells** (**MDCK** II) which is resistant to infection by the parent virus due to a lack of receptors. Inactivation of cellular receptors by either neuraminidase or acetylesterase and generation of receptors by resialylation of **cells** with N-acetyl-9-O-acetylneuraminic acid (Neu5,9Ac2) indicated that 9-O-acetylated **sialic** acid is a receptor determinant for both parent and **mutant** virus. The increased binding efficiency enabled the **mutant** to infect **cells** with a low content of 9-O-acetylated **sialic** acid which were resistant to the parent virus. By comparing the nucleotide sequences of the glycoprotein (HEF) genes of the parent and the **mutant** virus, only a single point mutation could be identified on the **mutant** gene. This mutation at nucleotide position 872 causes an amino acid exchange from threonine to isoleucine at position 284 on the amino acid sequence. Sequence similarity with a stretch of amino acids involved in the receptor-binding pocket of the **influenza** A hemagglutinin suggests that the mutation site on the **influenza** C glycoprotein (HEF) is part of the receptor-binding site.

L8 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1983:500272 HCAPLUS
DOCUMENT NUMBER: 99:100272
TITLE: Active **influenza** virus neuraminidase is expressed in **monkey cells** from cDNA cloned in **simian** virus 40 vectors
AUTHOR(S): Davis, Alan R.; Bos, Timothy J.; Nayak, Debi P.
CORPORATE SOURCE: Sch. Med., Univ. California, Los Angeles, CA, 90024, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1983), 80(13), 3976-80
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The late genes of SV40 virus were replaced with a cloned cDNA copy of the neuraminidase (NA; EC 3.2.1.18) [9001-67-6] gene of the WSN (H1N1) strain of human **influenza** virus. When the SV40-NA recombinant virus was complemented in a lytic infection of **monkey cells** with a helper virus containing an early region deletion mutatation, **influenza** NA was expressed and

readily detected by immunofluorescence, as well as by immunopptn. of in vivo-labeled proteins with monoclonal antibodies against NA. In addition, the expressed NA exhibited enzymic activity by cleaving the **sialic** acid residue from α-2,3-sialyllactitol [65907-88-2]. The expressed protein was glycosylated and transported to the **cell** surface, and it possessed the same mol. weight as the NA of WSN virus grown in **monkey cells**. Since the structure of NA is quite different from that of other integral membrane proteins and includes an anchoring region at the N-terminus, which consists of hydrophobic amino acids, deletion **mutants** of NA were constructed in this region. Replacement of DNA coding for the 1st 10 N-terminal amino acids with SV40 and linker sequences had no apparent effect on NA expression, glycosylation, transport to the **cell** surface, or enzymic activity. However, further deletion of NA DNA for the 1st 26 amino acids abolished NA expression. Thus, the hydrophobic N-terminal region is multifunctional and is important in biosynthesis and translocation of NA across the membrane as well as in anchoring the protein.

L8 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1981:404118 HCAPLUS
DOCUMENT NUMBER: 95:4118
TITLE: Glycosylation does not determine segregation of viral envelope proteins in the plasma membrane of epithelial **cells**
AUTHOR(S): Green, Reza F.; Meiss, Harriet K.; Rodriguez-Boulan, Enrique
CORPORATE SOURCE: Med. Sch., New York Univ., New York, NY, 10016, USA
SOURCE: Journal of Cell Biology (1981), 89(2), 230-9
CODEN: JCLBA3; ISSN: 0021-9525
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Enveloped viruses are excellent tools for the study of the biogenesis of epithelial polarity, because they bud asym. from confluent monolayers of epithelial **cells** and because polarized budding is preceded by the accumulation of envelope proteins exclusively in the plasma membrane regions from which the viruses bud. Three different exptl. approaches showed that the carbohydrate moieties do not determine the final surface localization of either **influenza** (WSN strain) or vesicular stomatitis virus (VSV) envelope proteins in infected **Madin-Darby Canine** Kidney (**MDCK**) **cells**, as determined by immunofluorescence and immunoelectron microscopy, using ferritin as a marker. Infected concanavalin A- and ricin I-resistant **mutants** of **MDCK cells**, with alterations in glycosylation, exhibited surface distributions of viral glycoproteins identical to those of the parental **cell** line, i.e., **influenza** envelope proteins were exclusively found in the apical surface, whereas VSV G protein was localized only in the basolateral region. **MDCK cells** treated with tunicamycin, which abolishes the glycosylation of viral glycoproteins, exhibited the same distribution of envelope proteins as control **cells**, after infection with VSV or **influenza**. A temperature-sensitive **mutant** of **influenza** WSN, ts3, which when grown at the nonpermissive temperature of 39.5° retains the **sialic**

acid residues in the envelope glycoproteins, showed, at both 32° (permissive temperature) and 39.5°, budding polarity and viral glycoprotein distribution identical to those of the parental WSN strain, when grown in **MDCK cells**. Thus, carbohydrate moieties are not components of the addressing signals that determine the polarized distribution of viral envelope proteins and, possibly of the intrinsic cellular plasma membrane proteins in the surface of epithelial **cells**.

L8 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1979:554211 HCAPLUS
DOCUMENT NUMBER: 91:154211
TITLE: Latex fetuin spheres as probes for **influenza** virus neuraminidase in productively and abortively infected **cells**
AUTHOR(S): Israel, A.; Niveleau, A.; Quash, G.; Richard, Marie Helene
CORPORATE SOURCE: Unite Virol., INSERM, Lyon, 69371/2, Fr.
SOURCE: Archives of Virology (1979), 61(3), 183-99
CODEN: ARVIDF; ISSN: 0304-8608
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fetuin-bound latex spheres did not adhere to the membranes of non-infected **cells** but adhered to those of **cells** productively infected by fowl plague virus (FPV Dobson strain). In contrast, asialofetuin spheres did not attach to the membranes of productively infected **cells**. Moreover, latex fetuin spheres incubated with exts. of productively infected **cells** and extensively washed were specifically enriched in neuraminidase (I) activity without any trace of hemagglutinin. Evidently, viral I in the membrane is the site of attachment of the **sialic** acid moieties of fetuin spheres. These I sites were detectable when L **cells** were productively infected by a **mammalian** **cell**-adapted **mutant** of the Dobson strain (FPV-B) but were not detectable on L **cells** abortively infected by wild-type (FPV+). However, even in the abortive system, I was synthesized de novo as shown by its labeling with glucosamine-14C and by its isolation from labeled exts. of infected **cells** by latex fetuin spheres. Thus, misintegration of viral I in the plasma membrane of L **cells** is a feature of abortive infection of these **cells** by the Dobson strain of FPV. However, the relation (if any) of this misintegration to abortive infection remains to be established.

L8 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1975:121600 HCAPLUS
DOCUMENT NUMBER: 82:121600
TITLE: Requirement of neuraminidase activity for **influenza** virus replication
AUTHOR(S): Palese, P.; Schulman, J. L.; Tobita, K.
CORPORATE SOURCE: Mt. Sinai Sch. Med., City Univ. New York, New York, NY, USA
SOURCE: Behring Institute Mitteilungen (1974), 55, 11-18
CODEN: BHIMA2; ISSN: 0301-0457
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The 1st series of expts. involved comparisons of 2 HON2

influenza virus recombinants derived by double infection of cloned viruses. The recombinants were identified and isolated with 2-(3'-methoxyphenyl)-**N-acetylneuraminic** acid (MPN). The HON2 (MPN+) virus had 8-10-fold more neuraminidase activity/mg of virus protein than HON2 (MPN-) virus. The greater quantity of neuraminidase in MPN+ virions was related to a greater rate of neuraminidase production in **cells** infected with MPN+ viruses. In a 2nd series of tests with the neuraminidase inhibitor 2-deoxy-2,3-dehydro-N-trifluoroacetylneuraminic acid (FANA) a wide variety of inhibitory concns. were found. This led to the conclusion that the inhibitory effects of FANA on virus replication are mediated by specific inhibition of neuraminidase activity, a clear demonstration that this activity is required for **influenza** virus replication. In a 3rd series of expts. 2 temperature-sensitive **mutants** of WSN virus were employed. Both of these **mutants** replicated in **bovine** kidney **cells** at the permissive temperature of 33° but at the nonpermissive temperature, 39.5°, the yield of infective virus in both cases was markedly reduced, and hemagglutination and neuraminidase activity was not demonstrable. It was concluded that although much more neuraminidase may be contained by **influenza** viruses than necessary for replication, at least some is essential. Thus, replication of **mutants** with temperature sensitive defects in neuraminidase or of wild type viruses in the presence of FANA are greatly impaired. Also, the primary function of neuraminidase may be to remove neuraminic acid from the virus thereby preventing aggregation of virus particles and consequent loss of infectivity.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, PHIC, PHIN, TOXCENTER, CABA, AGRICOLA, VETU, VETB' ENTERED AT 14:43:41 ON 18 DEC 2003)

L1	1	SEA FILE=REGISTRY ABB=ON PLU=ON "N-ACETYLNEURAMINIC ACID"/CN
L2	1	SEA FILE=REGISTRY ABB=ON PLU=ON "N-GLYCOLYLNEURAMINIC ACID"/CN
L3	2	SEA FILE=REGISTRY ABB=ON PLU=ON L1 OR L2
L4	22557	SEA FILE=HCAPLUS ABB=ON PLU=ON L3 OR SIALIC OR N(W)(ACETYLNEURAMINIC OR GLYCOLYLNEURAMINIC OR (ACETYL OR AC OR GLYCOLYL)(W)(NEU OR NEURAMINIC)) OR NEUNAC OR NEUGC
L11	2463	SEA L4 AND ((MAMMAL? OR SWINE OR PIG OR PIGLET OR HOG OR BOVINE OR OX OR COW OR CATTLE OR OX OR OXEN OR MONKEY OR SIMIAN OR APE OR CHIMP OR CHIMPANZ? OR CANINE OR DOG OR MDCK? OR MADIN DARBY OR MINK OR AVIAN OR BIRD)(S) CELL)
L12	265	SEA L11 AND (MUTANT OR MUTAGEN? OR POLYMORPH? OR POLY MORPH?)
L13	65	SEA L12 AND INFLUENZ?
L14	29	DUP REM L13 (36 DUPLICATES REMOVED)

L14 ANSWER 1 OF 29 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-706991 [76] WPIDS
DOC. NO. CPI: C2002-200568
TITLE: New **mutant** cell for propagating **influenza** virus with decreased sialidase activity useful as vaccine, comprises decreased levels of **sialic** acid containing host cell receptors for **influenza** virus.

DERWENT CLASS: B04 C06 D16
INVENTOR(S): KAWAOKA, Y
PATENT ASSIGNEE(S): (KAWA-I) KAWAOKA Y; (WISC) WISCONSIN ALUMNI RES FOUND
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002068632	A2	20020906	(200276)*	EN	33
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
US 2002197705	A1	20021226	(200304)		
EP 1364006	A2	20031126	(200380)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002068632	A2	WO 2002-US5455	20020222
US 2002197705	A1 Provisional	US 2001-271044P	20010223
		US 2002-81170	20020222
EP 1364006	A2	EP 2002-724994	20020222
		WO 2002-US5455	20020222

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1364006	A2 Based on	WO 2002068632

PRIORITY APPLN. INFO: US 2001-271044P 20010223; US 2002-81170 20020222
AN 2002-706991 [76] WPIDS
AB WO 200268632 A UPAB: 20021125
NOVELTY - An isolated **mutant** cell (I) comprising decreased levels of **sialic** acid containing host cell receptors for **influenza** virus relative to a corresponding wild-type cell which supports efficient **influenza** virus replication, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) isolating a cell that has decreased levels of receptors for **influenza** virus, comprising:

(a) contacting a population of cells permissive for **influenza** virus replication and sensitive to lectin or agglutinin growth inhibition with an amount of lectin or agglutinin to yield cells that are resistant to growth inhibition by the lectin or agglutinin that specifically binds **sialic** acid; and

(b) isolating a lectin- or agglutinin-resistant cell having decreased levels of receptors for **influenza** virus;

(2) a lectin- or agglutinin-resistant cell isolated by method (1);

(3) propagating **influenza** viruses having reduced sialidase activity by contacting (I) and the lectin- or agglutinin-resistant cell with an amount of an **influenza** virus having reduced sialidase activity to yield progeny virus;

(4) a progeny virus obtained by method (3);

(5) using a host cell having decreased levels of **sialic** acid containing host cell receptors for **influenza** virus, comprising:

(a) contacting (I) and the lectin- or agglutinin-resistant cell with an amount of an **influenza** virus having wild-type levels of sialidase activity to yield progeny virus; and

(b) serially propagating the progeny virus with (I) and the lectin- or agglutinin-resistant cell to yield adapted viruses that efficiently replicate in the **mutant** cell and the lectin- or agglutinin-resistant cell; and

(6) isolated adapted virus obtained by method (5), which does not have a mutation in the hemagglutinin (HA) gene relative to the virus having substantially wild-type levels of sialidase activity.

ACTIVITY - Virucide; Immunomodulator.

No biological data is given.

MECHANISM OF ACTION - Vaccine; Gene therapy.

USE - The **mutant** cell is useful in propagating **influenza** virus having reduced or decreased sialidase activity. The obtained virus may be employed in vaccines, in preparing monoclonal or polyclonal antibodies specific for those viruses, in preparing recombinant or reassortant viruses, or for gene delivery including the delivery of immunogenic non-**influenza** virus proteins or peptide for vaccines or therapeutic proteins.

Dwg.0/3

L14 ANSWER 2 OF 29 MEDLINE on STN DUPLICATE 1

ACCESSION NUMBER: 2002273351 MEDLINE
DOCUMENT NUMBER: 21988469 PubMed ID: 11991966
TITLE: In vitro selection and characterization of **influenza** A (A/N9) virus variants resistant to a novel neuraminidase inhibitor, A-315675.
AUTHOR: Molla Akhteruzzaman; Kati Warren; Carrick Robert; Steffy Kevin; Shi Yan; Montgomery Debra; Gusick Nanette; Stoll Vincent S; Stewart Kent D; Ng Teresa I; Maring Clarence; Kempf Dale J; Kohlbrenner William
CORPORATE SOURCE: Global Pharmaceutical Research and Development, Abbott Laboratories, Abbott Park, Illinois 60064, USA.. m.molla@abbott.com
SOURCE: JOURNAL OF VIROLOGY, (2002 Jun) 76 (11) 5380-6. Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020517
Last Updated on STN: 20020611
Entered Medline: 20020610

AB With the recent introduction of neuraminidase (NA) inhibitors into clinical practice for the treatment of **influenza** virus

infections, considerable attention has been focused on the potential for resistance development and cross-resistance between different agents from this class. A-315675 is a novel **influenza** virus NA inhibitor that has potent enzyme activity and is highly active in cell culture against a variety of strains of **influenza** A and B viruses. To further assess the therapeutic potential of this compound, in vitro resistance studies have been conducted and a comparative assessment has been made relative to oseltamivir carboxylate. The development of viral resistance to A-315675 was studied by in vitro serial passage of **influenza** A/N9 virus strains grown in **MDCK cells** in the presence of increasing concentrations of A-315675. Parallel passaging experiments were conducted with oseltamivir carboxylate, the active form of a currently marketed oral agent for the treatment of **influenza** virus infections. Passage experiments with A-315675 identified a variant at passage 8 that was 60-fold less susceptible to the compound. Sequencing of the viral population identified an E119D mutation in the NA gene, but no mutations were observed in the hemagglutinin (HA) gene. However, by passage 10 (2.56 microM A-315675), two mutations (R233K, S339P) in the HA gene appeared in addition to the E119D mutation in the NA gene, resulting in a 310-fold-lower susceptibility to A-315675. Further passaging at higher drug concentrations had no effect on the generation of further NA or HA mutations (20.5 microM A-315675). This P15 virus displayed 355-fold-lower susceptibility to A-315675 and >175-fold-lower susceptibility to zanamivir than did wild-type virus, but it retained a high degree of susceptibility to oseltamivir carboxylate. By comparison, virus variants recovered from passaging against oseltamivir carboxylate (passage 14) harbored an E119V mutation and displayed a 6,000-fold-lower susceptibility to oseltamivir carboxylate and a 175-fold-lower susceptibility to zanamivir than did wild-type virus. Interestingly, this **mutant** still retained susceptibility to A-315675 (42-fold loss). This suggests that cross-resistance between A-315675- and oseltamivir carboxylate-selected variants in vitro is minimal.

L14 ANSWER 3 OF 29 MEDLINE on STN DUPLICATE 2

ACCESSION NUMBER: 2002676126 MEDLINE
DOCUMENT NUMBER: 22276150 PubMed ID: 12388803
TITLE: A release-competent **influenza** A virus **mutant** lacking the coding capacity for the neuraminidase active site.
AUTHOR: Gubareva Larisa V; Nedyalkova Marina S; Novikov Dmitri V; Murti K Gopal; Hoffmann Erich; Hayden Frederick G
CORPORATE SOURCE: Department of Internal Medicine, University of Virginia, 1300 Jefferson Park Avenue, Jordan Hall Room 2231, PO Box 800473, Charlottesville 22908, USA.. LVG9B@virginia.edu
CONTRACT NUMBER: AI-45782 (NIAID)
SOURCE: JOURNAL OF GENERAL VIROLOGY, (2002 Nov) 83 (Pt 11) 2683-92.
Journal code: 0077340. ISSN: 0022-1317.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

OTHER SOURCE: GENBANK-AF398862; GENBANK-AF398864; GENBANK-AF398865; GENBANK-AF398866; GENBANK-AF398867; GENBANK-AF398870; GENBANK-AF398873; GENBANK-AF398874; GENBANK-AF398876; GENBANK-AF398877; GENBANK-AF398878
ENTRY MONTH: 200212
ENTRY DATE: Entered STN: 20021120
Last Updated on STN: 20021221
Entered Medline: 20021220

AB Both **influenza** A virus surface glycoproteins, the haemagglutinin (HA) and neuraminidase (NA), interact with neuraminic acid-containing receptors. The **influenza** virus A/Charlottesville/31/95 (H1N1) has shown a substantially reduced sensitivity to NA inhibitor compared with the A/WSN/33 (H1N1) isolate by plaque-reduction assays in **Madin-Darby canine** kidney (**MDCK**) **cells**. However, there was no difference in drug sensitivity in an NA inhibition assay. The replacement of the HA gene of A/WSN/33 with the HA gene of A/Charlottesville/31/95 led to a drastic reduction in sensitivity of A/WSN/33 to NA inhibitor in **MDCK cells**. Passage of A/Charlottesville/31/95 in cell culture in the presence of an NA inhibitor resulted in the emergence of **mutant** viruses (delNA) whose genomes lacked the coding capacity for the NA active site. The delNA **mutants** were plaque-to-plaque purified and further characterized. The delNA-31 **mutant** produced appreciable yields (approximately 10(6) p.f.u./ml) in **MDCK cell** culture supernatants in the absence of viral or bacterial NA activity. Sequence analysis of the delNA **mutant** genome revealed no compensatory substitutions in the HA or other genes compared with the wild-type. Our data indicate that sialylation of the oligosaccharide chains in the vicinity of the HA receptor-binding site of A/Charlottesville/31/95 virus reduces the HA binding efficiency and thus serves as a compensatory mechanism for the loss of NA activity. Hyperglycosylation of HA is common in **influenza** A viruses circulating in humans and has the potential to reduce virus sensitivity to NA inhibitors.

L14 ANSWER 4 OF 29 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002082758 EMBASE
TITLE: Use of pseudotyped retroviral vectors to analyze the receptor-binding pocket of hemagglutinin from a pathogenic avian **influenza** A virus (H7 subtype).
AUTHOR: Lin A.H.; Cannon P.M.
CORPORATE SOURCE: P.M. Cannon, Gene Therapy Laboratories, Norris Cancer Center, Univ. of S. CA Keck Sch. of Medicine, 1441 Eastlake Avenue, Los Angeles, CA 90033, United States. pcannon@hsc.usc.edu
SOURCE: Virus Research, (26 Feb 2002) 83/1-2 (43-56).
Refs: 33
ISSN: 0168-1702 CODEN: VIREDF
PUBLISHER IDENT.: S 0168-1702(01)00407-5
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The hemagglutinin (HA) protein of **influenza** virus binds to

terminal **sialic** acid residues present on **cell** surface glycoproteins and glycolipids. The specific amino acids involved in this interaction have been identified for a H3 subtype HA from the human non-pathogenic virus, A/Aichi/2/68, by both crystallographic and **mutagenesis** studies. We were interested to examine the receptor-binding pocket of a H7 subtype protein from the **avian** pathogenic virus A/FPV/Rostock/34. Accordingly, we made amino acid substitutions at six conserved residues (Y88, T126, H174, E181, L185, and G219), suggested by comparison with the receptor-binding pocket of the H3 protein, and analyzed the resulting proteins using pseudotyped retroviral vectors. The use of these vectors enabled us to quantitate both the ability of the **mutant** HA proteins to bind with receptor-expressing **cells**, and also to promote virus-**cell** fusion by measuring vector titer. Using this system, we identified a subset of **mutants** with impaired receptor-binding activity and a corresponding decrease in titer, but which retained the ability to induce syncytia in low pH **cell**-**cell** fusion assays. The most severely affected **mutants** contained more than one substitution, with the triple **mutant** Y88F/E181Q/G219K being the most defective. These observations highlight the importance of multiple contact points for the interaction between **sialic** acid and HA.

L14 ANSWER 5 OF 29 EMBASE on STN

ACCESSION NUMBER: 2001383131 EMBASE

TITLE: Hemagglutinin residues of recent human A(H3N2) **influenza** viruses that contribute to the inability to agglutinate chicken erythrocytes.

AUTHOR: Medeiros R.; Escriou N.; Naffakh N.; Manuguerra J.-C.; Van der Werf S.

CORPORATE SOURCE: S. Van der Werf, Unite Genet. Molec. des Virus Resp., Institut Pasteur, 25 rue du Dr Roux, 75724 Paris Cedex 15, France. svdwerf@pasteur.fr

SOURCE: Virology, (10 Oct 2001) 289/1 (74-85).
Refs: 60
ISSN: 0042-6822 CODEN: VIRLAX

COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB To identify the molecular determinants contributing to the inability of recent human **influenza** A(H3N2) viruses to agglutinate chicken erythrocytes, phenotypic revertants were selected upon passage in eggs or **MDCK cells**. The Leu194Ile or Val226Ile substitutions were detected in their hemagglutinin (HA) sequence concomitantly with the phenotypic reversion. Remarkably, as little as 3.5% of variants bearing a Val226Ile substitution was found to confer the ability to agglutinate chicken erythrocytes to the virus population. Hemadsorption assays following transient expression of mutated HA proteins showed that the successive Gln226 → Leu → Ile → Val changes observed on natural isolates resulted in a progressive loss of the ability of the HA to bind chicken erythrocytes. The Val226Ile change maintained the preference of the HA for SAα2,6Gal over SAα2,3Gal and

enhanced binding of the HA to α2,6Gal receptors present on chicken erythrocytes. In contrast, simultaneous Ser193Arg and Leu194Ile substitutions that were found to confer the ability to agglutinate sheep erythrocytes increased the affinity of the HA for SAα2,3Gal. .COPYRGT. 2001 Academic Press.

L14 ANSWER 6 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2001:443859 BIOSIS
DOCUMENT NUMBER: PREV200100443859
TITLE: Apoptosis by **influenza** viruses correlates with efficiency of viral mRNA synthesis.
AUTHOR(S): Stray, Stephen J.; Air, Gillian M. [Reprint author]
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, 73190, USA
gillian-air@ouhsc.edu
SOURCE: Virus Research, (September, 2001) Vol. 77, No. 1, pp. 3-17. print.
CODEN: VIREDF. ISSN: 0168-1702.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Sep 2001
Last Updated on STN: 22 Feb 2002

AB A **mutant influenza** virus, A/NWS-Mvi, grows well in the presence of exogenous sialidase activity sufficient to remove all cell surface **sialic** acids. Related wild-type viruses grow very poorly under these conditions, although **mutant** and wild-type viruses bind to desialylated cells with similar efficiency and show similar reduction of binding to sialidase-treated cells compared to native cells. Here we examine entry, transcription, translation, and RNA replication and find that, although the viruses appear to utilize the same entry pathway, the **mutant** NWS-Mvi transcribes and replicates RNA to higher levels than the wild-type strains. The kinetics of replication in multi-cycle infection show that this enhancement of RNA synthesis facilitates growth where entry is restricted. The hemagglutinin (HA) protein of NWS-Mvi lyses red blood cells 0.1 pH unit higher than wild-type viruses. This higher fusion pH may allow more efficient release of nucleocapsids from endosomes and contribute to the enhanced RNA synthesis. The efficient RNA synthesis assists virus survival at low inocula or under stringent growth conditions, such as the presence of antiviral agents. NWS-Mvi induces apoptosis in infected cells more readily than wild-type viruses, apparently as a consequence of enhanced production of viral mRNA. Since growth of NWS-Mvi is more efficient, apoptosis may play a positive role in viral replication by removing cells that have already been infected from those capable of making more virus.

L14 ANSWER 7 OF 29 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001192176 EMBASE
TITLE: Safe as mother's milk: Carbohydrates as future anti-adhesion drugs for bacterial diseases.
AUTHOR: Sharon N.; Ofek I.
CORPORATE SOURCE: N. Sharon, Department of Biological Chemistry, Weizmann Institute of Science, Rehovot 76100, Israel.

bfsharon@weizmann.weizmann.ac.il
SOURCE: Glycoconjugate Journal, (2000) 17/7-9 (659-664).
Refs: 24
ISSN: 0282-0080 CODEN: GLJOEW
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The majority of infectious diseases are initiated by adhesion of pathogenic organisms to the tissues of the host. In many cases, this adhesion is mediated by lectins present on the surface of the infectious organism that bind to complementary carbohydrates on the surface of the host tissues. Lectin-deficient **mutants** often lack ability to initiate infection. Soluble carbohydrates recognized by the bacterial lectins block the adhesion of the bacteria to animal **cells** in vitro. Moreover, they have also been shown to protect against experimental infection by lectin-carrying bacteria in different organs of **mammals** such as mice, rabbits, calves and **monkeys**. In a phase II clinical trial, a pentasaccharide shown to have anti-adhesive activity against Streptococcus pneumoniae and Hemophilus **influenzae** in vitro failed to protect young children from nasopharyngeal colonization with these organisms and from developing otitis media. This could be because insufficient drug was delivered via nasal spray, because bacteria express multiple specificities, the inhibition of which may require a cocktail of oligosaccharides, or because children have different carbohydrate receptors from those of adults. The results of a clinical trial in which N-acetylneuraminyl(α2-3)lactose was administered orally to Helicobacter pylori positive patients in an effort to reduce or eradicate bacterial colonization, are awaited with interest. Although the high cost of production of the required oligosaccharides is falling with the recent introduction of enzymatic methods of synthesis, new technologies, in particular the use of engineered bacteria, promise to lower it even further. Attachment of the oligosaccharides to soluble polymeric carriers will increase greatly their effectiveness as antiadhesion agents. There is no doubt that anti-adhesive oligosaccharides will in the near future join the arsenal of drugs for the therapy of bacterial diseases.

L14 ANSWER 8 OF 29 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2000454934 MEDLINE
DOCUMENT NUMBER: 20372558 PubMed ID: 10910970
TITLE: **Influenza** virus infection of desialylated cells.
AUTHOR: Stray S J; Cummings R D; Air G M
CORPORATE SOURCE: Department of Biochemistry & Molecular Biology, University of Oklahoma Health Sciences Center, Oklahoma City 73190, USA.
CONTRACT NUMBER: AI18203 (NIAID)
CA37626 (NCI)
SOURCE: GLYCOBIOLOGY, (2000 Jul) 10 (7) 649-58.
Journal code: 9104124. ISSN: 0959-6658.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000927

AB **Sialic** acid has long been considered to be the sole receptor for **influenza** virus. The viral hemagglutinin (HA) is known to bind cell surface **sialic** acid, and **sialic** acids on viral glyco-proteins are cleaved by the viral neuraminidase (NA) to promote efficient release of progeny virus particles. However, NWS-Mvi, a **mutant** virus completely lacking NA, grows well in **MDCK cells** continuously treated with exogenous neuraminidase (sialidase). Exogenous sialidase quantitatively releases all **sialic** acids from purified glycoproteins and glycolipids of **MDCK cells** and efficiently removes surface **sialic** acid from intact **cells**. Binding of NWS-Mvi and parent **influenza** viruses to **MDCK cells** is indistinguishable, and is only partially reduced by sialidase treatment of the **cells**. Both **mutant** and wild-type viruses enter enzymatically desialylated cells and initiate transcription. The ability of **influenza** A reassortant viruses to infect desialylated cells is shared by recent H3N2 clinical isolates, suggesting that this may be a general property of **influenza** A viruses. We propose that **influenza** virus infection can result from **sialic** acid-independent receptors, either directly or in a multistage process. When **sialic** acid is present, it may act to enhance virus binding to the cell surface to increase interaction with secondary receptors to mediate entry. Understanding virus entry will be critical to further efforts in infection control and prevention.

L14 ANSWER 9 OF 29 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2001102751 MEDLINE
DOCUMENT NUMBER: 20569541 PubMed ID: 11118381
TITLE: Change in receptor-binding specificity of recent human **influenza** A viruses (H3N2): a single amino acid change in hemagglutinin altered its recognition of sialyloligosaccharides.
AUTHOR: Nobusawa E; Ishihara H; Morishita T; Sato K; Nakajima K
CORPORATE SOURCE: Department of Virology, School of Nursing, Nagoya City University, Mizuho-cho, Mizuho-ku, Nagoya City, 467-8601, Japan.. nobusawa@med.nagoya-cu.ac.jp
SOURCE: VIROLOGY, (2000 Dec 20) 278 (2) 587-96.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010126

AB Human H3N2 **influenza** A viruses were known to preferentially bind to **sialic** acid (SA) in alpha2,6Gal

linkage on red blood cells (RBC). However, H3N2 viruses isolated in **MDCK cells** after 1992 did not agglutinate chicken RBC (CRBC). Experiments with point-mutated hemagglutinin (HA) of A/Aichi/51/92, one of these viruses, revealed that an amino acid change from Glu to Asp at position 190 (E190D) was responsible for the loss of ability to bind to CRBC. A/Aichi/51/92 did not agglutinate CRBC treated with alpha2, 3-sialidase, suggesting that SAalpha2,3Gal on CRBC might not inhibit the binding of the virus to SAalpha2,6Gal on CRBC. However, the virus agglutinated derivatized CRBC resialylated with SAalpha2, 6Galbeta1,4GlcNAc. These findings suggested that the E190D change might have rendered the HA able to distinguish sialyloligosaccharides on the derivatized CRBC containing the SAalpha2,6Galbeta1,4GlcNAc sequence from those on the native CRBC.

L14 ANSWER 10 OF 29 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 1999-243944 [20] WPIDS
DOC. NO. CPI: C1999-071160
TITLE: New lipid-containing vector with a **mutant** hemagglutinin, useful in gene therapy.
DERWENT CLASS: B04 D16
INVENTOR(S): BATES, P; MIR-SHEKARI, Y
PATENT ASSIGNEE(S): (UYPE-N) UNIV PENNSYLVANIA
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9913905	A1	19990325	(199920)*	EN	56
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP US					
AU 9893994	A	19990405	(199933)		
US 6416997	B1	20020709	(200253)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9913905	A1		WO 1998-US19552	19980917
AU 9893994	A		AU 1998-93994	19980917
US 6416997	B1	Provisional	US 1997-59239P	19970918
		Cont of	WO 1998-US19552	19980917
			US 2000-525392	20000315

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9893994	A	Based on	WO 9913905

PRIORITY APPLN. INFO: US 1997-59239P 19970918; US 2000-525392 20000315
AN 1999-243944 [20] WPIDS
AB WO 9913905 A UPAB: 19990525
NOVELTY - A lipid-containing vector (I) capable of fusing to a cell membrane.
DETAILED DESCRIPTION - The vector comprises hemagglutinin with

a mutation in the receptor binding pocket, abrogating binding to a **sialic** acid containing receptor but not affecting fusogenic capacity of the hemagglutinin.

INDEPENDENT CLAIMS are also included for the following:

(1) a method of producing a vector (II) comprising pseudotyping an enveloped virus with a **mutant influenza** A virus hemagglutinin which comprises at least one amino acid substitution at residues threonine-115, glutamin-190 and leucine-226 in the receptor binding pocket, and where the substitution abrogates binding of the hemagglutinin to a **sialic** acid containing receptor, and co-pseudotyping the virus with a targeting molecule.

(2) an isolated **influenza** A virus hemagglutinin (III) comprising a mutation which abrogates binding to a **sialic** acid containing receptor, but does not affect the fusogenic capability of hemagglutinin;

(3) DNA encoding an **influenza** A virus hemagglutinin with a mutation in the receptor binding pocket which abrogates binding to a **sialic** acid receptor, but does not affect fusogenic capabilities of the hemagglutinin;

(4) a pseudotyped murine leukemia virus (MLV) (IV) comprising a **mutant influenza** A virus hemagglutinin, the mutation comprising a change from threonine to serine at amino acid 155, and a change from leucine to valine at 226; the hemagglutinin expressed in the envelope of the pseudotyped MLV;

(5) a composition (V) comprising a co-pseudotyped enveloped virus expressing a **mutant** hemagglutinin and a targeting molecule, the co-pseudotyped virus binding to a target cell expressing a receptor for the targeting molecule, the hemagglutinin causing the virus to fuse with the cell; and

(6) **mammalian cells** comprising the pseudotyped MLV virus, or the co-pseudotyped virus (V).

USE - The new vectors are useful for targeted delivery of a component to a desired cell i.e. a nucleic acid, an antisense nucleic acid, a gene, a protein, a peptide, a Vpr protein, an enzyme, an intracellular antagonist of HIV, a radionuclide, a cytotoxic compound, an antiviral agent or an imaging agent (claimed) (i.e. gene therapy).

A cell-cell fusion assay between **mutant** and wild-type hemagglutinin showed that the new **mutant** was able to fuse with cells at the same levels as the wild-type, even though the receptor binding was abolished.

ADVANTAGE - Infectious titres of prior art retroviral vectors are low, and do not have an agent capable of inducing fusion of the virion envelope with the target cell membrane.

Dwg.0/12

L14 ANSWER 11 OF 29 MEDLINE on STN
ACCESSION NUMBER: 2000047978 MEDLINE
DOCUMENT NUMBER: 20047978 PubMed ID: 10580059
TITLE: An analysis of the role of neuraminidase in the receptor-binding activity of **influenza** B virus: the inhibitory effect of Zanamivir on haemadsorption.
AUTHOR: Luo C; Nobusawa E; Nakajima K
CORPORATE SOURCE: Department of Virology, Medical School, Nagoya City University, 1 Kawasumi, Mizuho-chou, Mizuho-ku, Nagoya 467, Japan.
SOURCE: JOURNAL OF GENERAL VIROLOGY, (1999 Nov) 80 (Pt 11)

2969-76.
Journal code: 0077340. ISSN: 0022-1317.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
ENTRY DATE: Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991215

AB We analysed the role of neuraminidase (NA) on haemadsorption by the haemagglutinin (HA) protein of **influenza** B virus. The **influenza** B virus **mutant** ts-7 has a temperature-sensitive mutation in the NA protein. At high temperature, cells infected with this virus did not exhibit haemadsorption activity, but the addition of bacterial neuraminidase (bNA) restored haemadsorption activity. COS cells transfected with HA cDNAs of B/Kanagawa/73 or B/Lee/40 virus showed no evidence of haemadsorption. However, with the addition of bNA or co-transfection with NA cDNA of the B/Lee/40 virus, haemadsorption was observed. Experiments with point-mutated HA cDNAs of B/Lee/40 virus showed that two N-acetyl glycosylation sites at amino acid residues 160 and 217 were responsible for the inability of the HA protein to adsorb to erythrocytes. These results indicated that haemadsorption by the HA protein of **influenza** B virus required the involvement of NA. Because the NA inhibitor Zanamivir was reported not to penetrate **cells**, we investigated the action of this inhibitor and found that Zanamivir inhibited haemadsorption on **MDCK cells** infected with B/Kanagawa/73 or B/Lee/40 virus. After removing Zanamivir by washing, the addition of bNA restored the haemadsorption activity on the infected cells. Scanning electron microscopy indicated that at 0.4 microM Zanamivir, HA protein did not adsorb to erythrocytes but retained the ability to aggregate virions. However, at 4 microM Zanamivir, distinct virion formation could not be observed.

L14 ANSWER 12 OF 29 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 1999054870 MEDLINE
DOCUMENT NUMBER: 99054870 PubMed ID: 9835519
TITLE: Characterization of human **influenza** virus variants selected in vitro in the presence of the neuraminidase inhibitor GS 4071.
AUTHOR: Tai C Y; Escarpe P A; Sidwell R W; Williams M A; Lew W; Wu H; Kim C U; Mendel D B
CORPORATE SOURCE: Research Virology, Gilead Sciences, Inc., Foster City, California 94404, USA.
CONTRACT NUMBER: NO1-AI-35178 (NIAID)
NO1-AI-65291 (NIAID)
SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1998 Dec) 42 (12) 3234-41.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990311
Last Updated on STN: 19990311

Entered Medline: 19990222

AB An oral prodrug of GS 4071, a potent and selective inhibitor of **influenza** neuraminidases, is currently under clinical development for the treatment and prophylaxis of **influenza** virus infections in humans. To investigate the potential development of resistance during the clinical use of this compound, variants of the human **influenza** A/Victoria/3/75 (H3N2) virus with reduced susceptibility to the neuraminidase inhibitor GS 4071 were selected in vitro by passaging the virus in **MDCK cells** in the presence of inhibitor. After eight passages, variants containing two amino acid substitutions in the hemagglutinin (A28T in HA1 and R124M in HA2) but no changes in the neuraminidase were isolated. These variants exhibited a 10-fold reduction in susceptibility to GS 4071 and zanamivir (GG167) in an in vitro plaque reduction assay. After 12 passages, a second variant containing these hemagglutinin mutations and a Lys substitution for the conserved Arg292 of the neuraminidase was isolated. The **mutant** neuraminidase enzyme exhibited high-level (30,000-fold) resistance to GS 4071, but only moderate (30-fold) resistance to zanamivir and 4-amino-Neu5Ac2en, the amino analog of zanamivir. The **mutant** enzyme had weaker affinity for the fluorogenic substrate 2'-(4-methylumbelliferyl)-alpha-D-**N-acetylneuraminic** acid and lower enzymatic activity compared to the wild-type enzyme. The viral variant containing the **mutant** neuraminidase did not replicate as well as the wild-type virus in culture and was 10,000-fold less infectious than the wild-type virus in a mouse model. These results suggest that although the R292K neuraminidase mutation confers high-level resistance to GS 4071 in vitro, its effect on viral virulence is likely to render this mutation of limited clinical significance.

L14 ANSWER 13 OF 29 MEDLINE on STN
ACCESSION NUMBER: 1998453440 MEDLINE
DOCUMENT NUMBER: 98453440 PubMed ID: 9780244
TITLE: Evidence for zanamivir resistance in an immunocompromised child infected with **influenza** B virus.
AUTHOR: Gubareva L V; Matrosovich M N; Brenner M K; Bethell R C; Webster R G
CORPORATE SOURCE: Department of Internal Medicine, University of Virginia, Charlottesville, USA.
CONTRACT NUMBER: AI-08831 (NIAID)
AI-33898 (NIAID)
CA-21765 (NCI)
SOURCE: JOURNAL OF INFECTIOUS DISEASES, (1998 Nov) 178 (5) 1257-62.
Journal code: 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981210

AB Zanamivir, a neuraminidase inhibitor, has shown promise as a drug to control **influenza**. During prolonged treatment with

zanamivir, a **mutant** virus was isolated from an immunocompromised child infected with **influenza** B virus. A hemagglutinin mutation (198 Thr-->Ile) reduced the virus affinity for receptors found on susceptible human cells. A mutation in the neuraminidase active site (152 Arg-->Lys) led to a 1000-fold reduction in the enzyme sensitivity to zanamivir. When tested in ferrets, the **mutant** virus had less virulence than the parent; however, it had a growth preference over the parent in zanamivir-treated animals. Despite these changes, the sensitivity of the **mutant** virus to zanamivir assessed by a standard test in **MDCK cells** was unaffected. These data indicate that the current methods for monitoring resistant **mutants** are potentially flawed because no tissue culture system adequately reflects the receptor specificity of human respiratory tract epithelium.

L14 ANSWER 14 OF 29 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 1998218688 MEDLINE
DOCUMENT NUMBER: 98218688 PubMed ID: 9559786
TITLE: Generation and characterization of a **mutant** of **influenza** A virus selected with the neuraminidase inhibitor BCX-140.
AUTHOR: Bantia S; Ghate A A; Ananth S L; Babu Y S; Air G M; Walsh G M
CORPORATE SOURCE: BioCryst Pharmaceuticals, Inc., Birmingham, Alabama 35244, USA.. sbantia@biocryst.com
CONTRACT NUMBER: AI-18203 (NIAID)
SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1998 Apr) 42 (4) 801-7.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980708
Last Updated on STN: 19980708
Entered Medline: 19980622

AB **Influenza** neuraminidase (NA) plays an important role in viral replication, and characterization of viruses resistant to NA inhibitors will help elucidate the role of active-site residues. This information will assist in designing better inhibitors targeted to essential active-site residues that cannot generate drug-resistant mutations. In the present study we used the benzoic acid-based inhibitor BCX-140 to select and characterize resistant viruses. BCX-140 binds to the NA active site in an orientation that is opposite that of a **sialic** acid-based compound, 4-guanidino-2,4-dideoxy-2,3-dehydro-**N-acetylneuraminic** acid (GANA). Thus, the guanidino group of BCX-140 binds to Glu-276, whereas in GANA the guanidino group binds to Glu-119. We passaged **influenza** A/Singapore/1/57 (H2N2) in **Madin-Darby canine** kidney **cells** in the presence of BCX-140, and virus resistant to this inhibitor was selected after six passages. The NA of this **mutant** was still sensitive to inhibition by BCX-140. However, the **mutant** virus was resistant to BCX-140 in plaque and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays. Sequence analysis of hemagglutinin (HA) and

NA genes revealed changes in both, although none were in the active site of the NA. Depending on the method of selection of the resistant virus, two types of changes associated with the **sialic** acid binding site were seen in the HA. One is a change in HA1 of Ala-133 to Thr, a residue close to the binding site, while the other change was Arg-132 of HA1 to Gln, which in HA1 of serotype H3 is a **sialic** acid contact (Asn-137). Binding studies revealed that both types of resistant viruses had reduced receptor binding affinity compared to that of the wild type. Thus, resistance to BCX-140 was generated by modifying the HA. NA active-site residue 276 may be essential for activity, and thus, it cannot be changed to generate resistance. However, drug-induced changes in the HA can result in a virus that is less dependent on NA activity for growth in cells and, hence, resistant to NA inhibitors.

L14 ANSWER 15 OF 29 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 1998371441 MEDLINE
DOCUMENT NUMBER: 98371441 PubMed ID: 9705915
TITLE: Differences in the biological phenotype of low-yielding (L) and high-yielding (H) variants of swine **influenza** virus A/NJ/11/76 are associated with their different receptor-binding activity.
AUTHOR: Gambaryan A S; Matrosovich M N; Bender C A; Kilbourne E D
CORPORATE SOURCE: M.P. Chumakov Institute of Poliomyelitis and viral Encephalitides, Russian Academy of Medical Sciences, Moscow, Russia.
SOURCE: VIROLOGY, (1998 Aug 1) 247 (2) 223-31.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980903
Last Updated on STN: 19980903
Entered Medline: 19980827

AB Low- (L) and high-yielding (H) variants of A/sw/NJ/11/76 **influenza** virus were compared for their growth properties in embryonated chicken eggs and **MDCK cells** and for their binding affinity for the membrane fractions prepared from **cells** of the chicken embryo allantoic membrane. **MDCK**, and **swine** tracheal **cells**, as well as for soluble **sialic** acid containing macromolecules and monovalent sialosides. We have shown, that during infection in **MDCK cells** and in eggs, the progeny of the L variant remain predominantly **cell** associated, in contrast to those of H. As a result, accumulation of the L **mutant** in allantoic or culture fluid is significantly slowed in comparison with the H variant. Visualization of the infectious foci formed by the viruses in **MDCK cell** monolayers and on the allantoic membrane revealed that L spreads predominantly from **cell** to **cell**, while the spread of H involves release of the virus progeny into solution and its rapid distribution over the **cell** monolayer via convectional flow of the liquid. In the binding assays, L displayed significantly higher binding affinity than H for cellular membranes, gangliosides,

and sialylglycoproteins, however, the affinity of the variants for the monovalent **sialic** acid compounds was comparable. Unlike H. L bound strongly to dextran sulfate. The data obtained suggest that all distinctions of the L and H biological phenotypes reported previously [Kilbourne, E.D., Taylor, A. H. Whitaker, C.W., Sahai, R., and Caton, A (1988) Hemagglutinin **polymorphism** as the basis for low-and high-yield phenotypes of swine **influenza** virus. Proc. Natl. Acad. Sci. USA 85, 7782-7785] could be rationally explained by a more avid binding of the L variant to the surface of target cells, and that this effect is mainly due to enhanced electrostatic interactions.

L14 ANSWER 16 OF 29 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1998122995 MEDLINE
DOCUMENT NUMBER: 98122995 PubMed ID: 9454721
TITLE: Studies of the binding properties of **influenza** hemagglutinin receptor-site **mutants.**
AUTHOR: Martin J; Wharton S A; Lin Y P; Takemoto D K; Skehel J J; Wiley D C; Steinhauer D A
CORPORATE SOURCE: Division of Virology, National Institute for Medical Research, The Ridgeway, Mill Hill, London, NW7 1AA, United Kingdom.
CONTRACT NUMBER: AI-13654 (NIAID)
SOURCE: VIROLOGY, (1998 Feb 1) 241 (1) 101-11. Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980306
Last Updated on STN: 19980306
Entered Medline: 19980226

AB Site-specific mutations have been made in the **influenza** hemagglutinin (HA) receptor binding site to assess the contribution of individual amino acid residues to receptor recognition. Screening of **mutant** HAs, expressed using recombinant vaccinia virus-infected cells, for their abilities to bind human erythrocytes indicated that substitutions involving conserved residues Y98F, H183F, and L194A severely restricted binding and that the substitution W153A prevented cell surface expression of HA. Mutation of residues E190 and S228 that are in positions to form hydrogen bonds with the 9-OH of **sialic** acid appeared to increase erythrocyte binding slightly, as did the substitution G225R. Substitutions of other residues that are directly or indirectly involved in receptor binding, S136T, S136A, Y195F, G225D, and L226P, had intermediate effects on binding between these two extremes. Estimates of changes in receptor binding specificity based on inhibition of binding to erythrocytes by nonimmune horse sera indicated that **mutants** G225R and L226P, unlike wild-type HA, were not inhibited; Y195F and G225D **mutants** were, like wild type, inhibited; and erythrocyte binding by **mutants** S136A, S136T, E190A, and S228G was only partially inhibited. Viruses containing **mutant** HAs Y98F, S136T, G225D, and S228G that cover the range of erythrocyte binding properties observed were also constructed by transfection. All four transfectant viruses replicated in **MDCK cells**

and embryonated hens' eggs as efficiently as wild-type X-31 virus, although the Y98F **mutant** virus was unable to agglutinate erythrocytes. **Mutant MDCK cells** that have reduced levels of **cell** surface **sialic** acids were susceptible to infection by S136T, G225D, and S228G transfectant viruses and by wild type but not by the Y98F transfectant virus.

L14 ANSWER 17 OF 29 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 97248379 MEDLINE
DOCUMENT NUMBER: 97248379 PubMed ID: 9094607
TITLE: Catalytic and framework mutations in the neuraminidase active site of **influenza** viruses that are resistant to 4-guanidino-Neu5Ac2en.
AUTHOR: Gubareva L V; Robinson M J; Bethell R C; Webster R G
CORPORATE SOURCE: Department of Virology/Molecular Biology, St. Jude Children's Research Hospital, Memphis, Tennessee 38101, USA.. larisa.gubareva@stjude.org
CONTRACT NUMBER: AI-08831 (NIAID)
CA-21765 (NCI)
SOURCE: JOURNAL OF VIROLOGY, (1997 May) 71 (5) 3385-90.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970507
Last Updated on STN: 19990129
Entered Medline: 19970425

AB Here we report the isolation of **influenza** virus A/turkey/Minnesota/833/80 (H4N2) with a mutation at the catalytic residue of the neuraminidase (NA) active site, rendering it resistant to the novel NA inhibitor 4-guanidino-Neu5Ac2en (GG167). The resistance of the **mutant** stems from replacement of one of three invariant arginines (Arg 292-->Lys) that are conserved among all viral and bacterial NAs and participate in the conformational change of **sialic** acid moiety necessary for substrate catalysis. The Lys292 **mutant** was selected in vitro after 15 passages at increasing concentrations of GG167 (from 0.1 to 1,000 microM), conditions that earlier gave rise to GG167-resistant **mutants** with a substitution at the framework residue Glu119. Both types of **mutants** showed similar degrees of resistance in plaque reduction assays, but the Lys292 **mutant** was more sensitive to the inhibitor in NA inhibition tests than were **mutants** bearing a substitution at framework residue 119 (Asp, Ala, or Gly). Cross-resistance to other NA inhibitors (4-amino-Neu5Ac2en and Neu5Ac2en) varied among **mutants** resistant to GG167, being lowest for Lys292 and highest for Asp119. All GG167-resistant **mutants** demonstrated markedly reduced NA activity, only 3 to 50% of the parental level, depending on the particular amino acid substitution. The catalytic **mutant** (Lys292) showed a significant change in pH optimum of NA activity, from 5.9 to 5.3. All of the **mutant** NAs were less stable than the parental enzyme at low pH. Despite their impaired NA activity, the GG167-resistant **mutants** grew as well as parental virus in **Madin**-

Darby canine kidney **cells** or in embryonated chicken eggs. However, the infectivity in mice was 500-fold lower for Lys292 than for the parental virus. These findings demonstrate that amino acid substitution in the NA active site at the catalytic or framework residues, followed by multiple passages in vitro, in the presence of increasing concentrations of the NA inhibitor GG167, generates GG167-resistant viruses with reduced NA activity and decreased infectivity in animals.

L14 ANSWER 18 OF 29 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 97085205 EMBASE
DOCUMENT NUMBER: 1997085205
TITLE: Differences in **sialic** acid-galactose linkages in the chicken egg amnion and allantois influence human **influenza** virus receptor specificity and variant selection.
AUTHOR: Ito T.; Suzuki Y.; Takada A.; Kawamoto A.; Otsuki K.; Masuda H.; Yamada M.; Suzuki T.; Kida H.; Kawaoka Y.
CORPORATE SOURCE: Y. Kawaoka, Dept. of Virology/Molecular Biology, St. Jude Children's Research Hosp., 332 N. Lauderdale, Memphis, TN 38101-0318, United States. yoshi.kawaoka@stjude.org
SOURCE: Journal of Virology, (1997) 71/4 (3357-3362). Refs: 35
ISSN: 0022-538X CODEN: JOVIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Human **influenza** viruses are more efficiently isolated by inoculating patient samples into the amniotic rather than the allantoic cavity of embryonated chicken eggs. This type of cultivation selects virus variants with mutations around the hemagglutinin (HA) receptor binding site. To understand the molecular basis of these phenomena, we investigated the abundances of **sialic** acid (SA) linked to galactose (Gal) by the α-2,3 linkage (SAα2,3Gal) and SAα2,6Gal in egg amniotic and allantoic **cells** and in **Madin-Darby canine** kidney (**MDCK**) **cells**. Using SA-Gal linkage-specific lectins (Maackia amurensis agglutinin specific for SAα2,6Gal and Sambucus nigra agglutinin specific for SAα2,3Gal), we found SAα2,3Gal in both allantoic and amniotic **cells** and SAα2,6Gal in only the amniotic **cells**. **MDCK cells** contained both linkages. To investigate how this difference in abundances of SAα2,3Gal and SAα2,6Gal in allantoic and amniotic **cells** affects the appearance of host **cell** variants in eggs, we determined the receptor specificities and HA amino acid sequences of two different patient viruses which were isolated and passaged in the amnion or in the allantois and which were compared with **MDCK cell**-grown viruses. We found that the viruses maintained high SAα2,6Gal specificities when grown in **MDCK cells** or following up to two amniotic passages; however, further passages in either the amnion or allantois resulted in the acquisition of, or a complete shift to, SAα2,3Gal specificity, depending on the virus strain. This

change in receptor specificity was accompanied by the appearance of variants in the population with Leu-to-Gln mutations at position 226 in their HA. These findings suggest that lack of SAα2,6Gal linkages in the allantois of chicken eggs is a selective pressure for the appearance of host **cell** variants with altered receptor specificities and amino acid changes at position 226.

L14 ANSWER 19 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1997:167208 BIOSIS
DOCUMENT NUMBER: PREV199799473811
TITLE: Hemagglutinin specificity and neuraminidase coding capacity of neuraminidase-deficient **influenza** viruses.
AUTHOR(S): Yang, Ping [Reprint author]; Bansal, Anju; Liu, Chongguang; Air, Gillian M.
CORPORATE SOURCE: Dep. Biochemistry Mol. Biol., Univ. Oklahoma Health Sci. Cent., PO Box 26901, Oklahoma City, OK 73190, USA
SOURCE: Virology, (1997) Vol. 229, No. 1, pp. 155-165. CODEN: VIRLAX. ISSN: 0042-6822.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Apr 1997
Last Updated on STN: 24 Apr 1997

AB Neuraminidase (NA)-deficient **mutant** virus stocks have been obtained by passaging A/NWS/33-HA-tern/Australia/G70c/75-NA (H1N9) **influenza** virus in medium containing neuraminidase from Micromonospora viridifaciens and antiserum against the **influenza** NA. Growth of the resulting **mutants** is dependent on addition of bacterial neuraminidase to the medium. Nucleotide sequence analysis showed large single deletions in the NA genes, with both ends of the NA gene segments conserved. These RNA fragments all have the capacity to code for a peptide that contains the N-terminal "tail" and membrane-anchoring region of the NA, but the presence of this peptide has not been demonstrated in virions or infected cells. In contrast to the ease of selection of NA-deficient **mutants** from the H1N9 virus, no **mutants** were selected from three other viruses. The HA-coding segments of parental H1N9 and **mutant** NWSc-Mvi predict a change of Pro to His at residue 227 (H3 numbering), close to the receptor-binding site of H3 HA, compared to the HA of an H1N2 reassortant that contains the NWS/33 HA gene. This change may contribute to an altered HA specificity that allows selection of **mutants** that can infect cells in the presence of high levels of NA activity. It appears that the role of NA in **influenza** infection is to remove **sialic** acid from the HA rather than to destroy receptors on cells.

L14 ANSWER 20 OF 29 MEDLINE on STN DUPLICATE 10

ACCESSION NUMBER: 96190584 MEDLINE
DOCUMENT NUMBER: 96190584 PubMed ID: 8627706
TITLE: Characterization of **mutants** of **influenza** A virus selected with the neuraminidase inhibitor 4-guanidino-Neu5Ac2en.
AUTHOR: Gubareva L V; Bethell R; Hart G J; Murti K G; Penn C R; Webster R G
CORPORATE SOURCE: Department of Virology/Molecular Biology, St Jude

Children's Research Hospital, Memphis, Tennessee 38101, USA.
CONTRACT NUMBER: AI-08831 (NIAID)
CA-21765 (NCI)
SOURCE: JOURNAL OF VIROLOGY, (1996 Mar) 70 (3) 1818-27.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960708
Last Updated on STN: 19990129
Entered Medline: 19960627

AB The development of viral resistance to the neuraminidase (NA) inhibitor, 4-guanidino-Neu5Ac2en, of **influenza** viruses was studied by serial passage of A/Turkey/Minnesota/833/80 (H4N2) in **Madin-Darby canine** kidney **cells** in the presence of increasing concentrations of inhibitor. Resistant **mutants** selected after eight passages, had a 10,000-fold reduction in sensitivity to the inhibitor in plaque assays, but their affinity (1/Kd) to the inhibitor was similar to that of the parental virus. Electron microscopic analysis revealed aggregation of the **mutant** virus at the cell surface in the presence of the inhibitor. Sequence analysis established that a substitution had occurred in the NA (Arg-249 to Lys) and in the HA2 subunit of the hemagglutinin (Gly-75 to Glu), in the vicinity of the proposed second **sialic** acid binding site. The change of residue 249 appears to be a chance mutation, for we were unable to reisolate this **mutant**, whereas subsequent experiments indicate changes in the hemagglutinin. After 13 passages of the parental virus, **mutants** that were resistant to the high concentrations of inhibitor tested were obtained. These viruses retained their drug-resistant phenotype even after five passages without the inhibitor. Electron microscopic analysis revealed no aggregation of virus on the surface of infected cells in the presence of the inhibitor. Sequence analysis of the NA gene from these drug-resistant **mutants** revealed an additional substitution of Glu to Ala at the conserved amino acid residue 119. This substitution is responsible for reducing the affinity of the inhibitor to the NA. Our findings suggest that the emergence of **mutants** resistant to 4-guanidine-Neu5Ac2en is a multistep process requiring prolonged exposure to the inhibitor.

L14 ANSWER 21 OF 29 MEDLINE on STN DUPLICATE 11
ACCESSION NUMBER: 96030862 MEDLINE
DOCUMENT NUMBER: 96030862 PubMed ID: 7595356
TITLE: The catalytic triad of the **influenza** C virus glycoprotein HEF esterase: characterization by site-directed **mutagenesis** and functional analysis.
AUTHOR: Pleschka S; Klenk H D; Herrler G
CORPORATE SOURCE: Institut fur Virologie, Philipps-Universitat Marburg, Germany.
SOURCE: JOURNAL OF GENERAL VIROLOGY, (1995 Oct) 76 (Pt 10) 2529-37.
Journal code: 0077340. ISSN: 0022-1317.
PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 20000303
Entered Medline: 19951128

AB **Influenza** C virus is able to inactivate its own cellular receptors by virtue of a sialate 9-O-acetylesterase that releases the acetyl residue at position C-9 of N-acetyl-9-O-acetylneuraminic acid (Neu5,9Ac2). The receptor-destroying enzyme activity is a function of the surface glycoprotein HEF and this esterase belongs to the class of serine hydrolases. In their active site, these enzymes contain a catalytic triad made up of a serine, a histidine and an aspartic acid residue. Sequence comparison with other serine esterases has indicated that, in addition to serine-71 (S71), the amino acids histidine-368 or -369 (H368/369) and aspartic acid 261 (D261) are the most likely candidates to form the catalytic triad of the **influenza** C virus glycoprotein. By site-directed **mutagenesis, mutants** were generated in which alanine substituted for either of these amino acids. Using a phagemid expression vector, pSP1D-HEF the HEF gene was expressed in both COS 7 and **MDCK** I **cells**. The glycoprotein was obtained in a functional form only in the latter cells, as indicated by its transport to the cell surface and measurable enzyme activity. The low level of expression could be increased by stimulating the NF-KB-binding activity of the cytomegalovirus immediate-early promoter/enhancer element of the vector. The esterase activity of the **mutant** proteins was compared with that of the wild-type glycoprotein. With Neu5,9Ac2 as the substrate, the esterase specific activities of the S71/A **mutant** and the H368,369/A **mutant** were reduced by more than 90%. In the case of the D261/A **mutant** the specific activity was reduced by 64%. From this data we conclude that S71, H368/369 and D261 are likely to represent the catalytic triad of the **influenza** C virus glycoprotein HEF. In addition, N280 is proposed to stabilize the oxyanion of the presumptive transition state intermediate formed by the enzyme-substrate complex.

L14 ANSWER 22 OF 29 MEDLINE on STN DUPLICATE 12
ACCESSION NUMBER: 95407118 MEDLINE
DOCUMENT NUMBER: 95407118 PubMed ID: 7676651
TITLE: Neuraminidase is essential for fowl plague virus hemagglutinin to show hemagglutinating activity.
AUTHOR: Ohuchi M; Feldmann A; Ohuchi R; Klenk H D
CORPORATE SOURCE: Institut fur Virologie, Philipps-Universitat Marburg, Germany.
SOURCE: VIROLOGY, (1995 Sep 10) 212 (1) 77-83.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951026
Last Updated on STN: 19951026
Entered Medline: 19951013

AB When hemagglutinin (HA) of fowl plague virus (FPV) was expressed in CV-1 **cells** by a **simian** virus 40 vector, hemadsorption was barely detectable, although HA was exposed at the **cell** surface. However, treatment of HA-expressing cells with Vibrio cholerae neuraminidase (VCNA) resulted in extensive hemadsorption. VCNA treatment enhanced the electrophoretic mobility of the HA1 subunit of HA, indicating the removal of **sialic** acid. When two oligosaccharides in the vicinity of the receptor binding site of FPV HA were deleted by site-specific **mutagenesis**, VCNA treatment was not required for hemadsorption. **Mutants** which retained one of these oligosaccharides and **mutants** in which oligosaccharides not adjacent to the receptor binding site were deleted needed VCNA treatment to show hemadsorption. VCNA treatment also enhanced hemadsorption of vector-expressed HA of the WSN strain, which had a complex-type oligosaccharide in the vicinity of the receptor binding site, but had no effect on hemadsorption of Hong Kong type HA, which has a high-mannose type oligosaccharide adjacent to the receptor binding site. These results indicate that **sialic** acid on oligosaccharides near the receptor binding site interferes with hemadsorption. Thus, the neuraminidase is essential for FPV HA to show hemagglutinating activity.

L14 ANSWER 23 OF 29 EMBASE on STN

ACCESSION NUMBER: 94289250 EMBASE
DOCUMENT NUMBER: 1994289250
TITLE: Persistent **influenza** C virus possesses distinct functional properties due to a modified HEF glycoprotein.
AUTHOR: Marschall M.; Herrler G.; Boswald C.; Foerst G.; Meier-Ewert H.
CORPORATE SOURCE: Abteilung fur Virologie, Inst Medizinische Mikrobiol Hygiene, Technische Universitat Munchen, Biedersteiner Strasse 29,DW-80802 Munchen, Germany
SOURCE: Journal of General Virology, (1994) 75/9 (2189-2196). ISSN: 0022-1317 CODEN: JGVIAY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A model of long term viral persistence has been established by selecting a spontaneous **mutant** strain of **influenza** C/Ann Arbor/1/50 virus in a permanent carrier culture of **MDCK cells**. Infectivity and **cell** tropism are mainly determined by the multifunctional viral membrane glycoprotein (HEF). HEF analysis was aimed at identifying a putative correlation between sequence and function, i.e. receptor binding, enzymatic activity, antigenicity and rate of infection. The current experimental picture is summarized by the following findings: (i) C/Ann Arbor/1/50 persistent virus carries a modified receptor-binding sequence, (ii) receptor-binding activity is altered, as indicated by a higher efficiency in recognizing low amounts of the receptor determinant N-acetyl-9-O-acetylneuraminic acid, (iii) direct attachment to **cell** surfaces differs from that of wild-type virus, as measured by slower kinetics of

viral elution, (iv) receptor-destroying enzymatic activity is diminished, (v) characteristic features of virion surface morphology are altered or unstable, (vi) persistent-type HEF epitopes are distinguishable by monoclonal antibodies from wild-type and (vii) viral infectivity is intensified for **cells** bearing a low number of receptors. The sum of these changes highlights a structurally and functionally modified HEF glycoprotein that allows long term viral persistence. In order to clarify which of the described points are required for the persistent viral phenotype, a working concept is presented.

L14 ANSWER 24 OF 29 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 94025940 MEDLINE
DOCUMENT NUMBER: 94025940 PubMed ID: 8212856
TITLE: Alterations of the stalk of the **influenza** virus neuraminidase: deletions and insertions.
COMMENT: Erratum in: Virus Res. 1993 Sep;29(3):321
AUTHOR: Luo G; Chung J; Palese P
CORPORATE SOURCE: Microbiology Department, Mount Sinai School of Medicine, New York, NY 10029.
SOURCE: VIRUS RESEARCH, (1993 Aug) 29 (2) 141-53. Journal code: 8410979. ISSN: 0168-1702.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199311
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19970203
Entered Medline: 19931115

AB The neuraminidase (NA) of **influenza** viruses cleaves **sialic** acids from receptors, prevents self-aggregation and facilitates release of virus during budding from host cells. Although the structure and function of the globular head of the **influenza** virus NA has been well studied, much less is known about the stalk of the NA, the region between the viral membrane and the globular head. Applying a reverse genetics system, we altered the stalk of the **influenza** A/WSN/33 virus NA by making deletions, insertions and mutations in this region of the gene. Our data show that the length of the NA stalk can be variable. Deletions of up to 28 amino acids and insertions of up to 41 amino acids in the stalk region did not abolish formation of infectious progeny virus. The data also indicate that the cysteine at position 76 is essential for formation of infectious virus, and that deletions beyond the cysteine did not result in infectious virus. Interestingly, shortening of the length of the stalk region by 28 amino acids resulted in a virus with a markedly reduced growth rate in **MDCK cells** as compared to that in MDBK **cells**. An insertion of 41 extra amino acids into the stalk did not significantly interfere with viral growth in **MDCK** or MDBK **cells**, which suggests that the stalk region would tolerate the introduction of long foreign sequences.

L14 ANSWER 25 OF 29 MEDLINE on STN DUPLICATE 14
ACCESSION NUMBER: 92230251 MEDLINE
DOCUMENT NUMBER: 92230251 PubMed ID: 1566586
TITLE: A single point mutation of the **influenza** C virus glycoprotein (HEF) changes the viral

receptor-binding activity.

AUTHOR: Szepanski S; Gross H J; Brossmer R; Klenk H D; Herrler G

CORPORATE SOURCE: Institut fur Virologie, Philipps-Universitat Marburg, Germany.

SOURCE: VIROLOGY, (1992 May) 188 (1) 85-92.
Journal code: 0110674. ISSN: 0042-6822.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199205

ENTRY DATE: Entered STN: 19920607
Last Updated on STN: 19970203
Entered Medline: 19920515

AB From strain JHB/1/66 of **influenza** C virus a **mutant** was derived with a change in the cell tropism. The **mutant** was able to grow in a subline of **Madin-Darby canine** kidney **cells** (**MDCK** II) which is resistant to infection by the parent virus due to a lack of receptors. Inactivation of cellular receptors by either neuraminidase or acetylesterase and generation of receptors by resialylation of cells with N-acetyl-9-O-acetylneuraminic acid (Neu5,9Ac2) indicated that 9-O-acetylated **sialic** acid is a receptor determinant for both parent and **mutant** virus. However, the **mutant** required less Neu5,9Ac2 on the cell surface for virus attachment than the parent virus. The increased binding efficiency enabled the **mutant** to infect cells with a low content of 9-O-acetylated **sialic** acid which were resistant to the parent virus. By comparing the nucleotide sequences of the glycoprotein (HEF) genes of the parent and the **mutant** virus only a single point mutation could be identified on the **mutant** gene. This mutation at nucleotide position 872 causes an amino acid exchange from threonine to isoleucine at position 284 on the amino acid sequence. Sequence similarity with a stretch of amino acids involved in the receptor-binding pocket of the **influenza** A hemagglutinin suggests that the mutation site on the **influenza** C glycoprotein (HEF) is part of the receptor-binding site.

L14 ANSWER 26 OF 29 MEDLINE on STN DUPLICATE 15

ACCESSION NUMBER: 83247400 MEDLINE

DOCUMENT NUMBER: 83247400 PubMed ID: 6306656

TITLE: Active **influenza** virus neuraminidase is expressed in **monkey cells** from cDNA cloned in **simian** virus 40 vectors.

AUTHOR: Davis A R; Bos T J; Nayak D P

CONTRACT NUMBER: AI-12749 (NIAID)
AI-16348 (NIAID)
GM-07104 (NIGMS)

SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1983 Jul) 80 (13) 3976-80.
Journal code: 7505876. ISSN: 0027-8424.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 198308
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19830811

AB We have replaced the late genes of simian virus 40 (SV40) with a cloned cDNA copy of the neuraminidase (NA; EC 3.2.1.18) gene of the WSN (H1N1) strain of human **influenza** virus. When the SV40-NA recombinant virus was complemented in a lytic infection of **monkey cells** with a helper virus containing an early region deletion **mutant**, **influenza** NA was expressed and readily detected by immunofluorescence as well as by immunoprecipitation of in vivo labeled proteins with monoclonal antibodies against NA. In addition, the expressed NA exhibited enzymatic activity by cleaving the **sialic** acid residue from alpha-2,3-sialyllactitol. The expressed protein was glycosylated and transported to the **cell** surface, and it possessed the same molecular weight as the NA of WSN virus grown in **monkey cells**. Because the structure of NA is quite different from that of other integral membrane proteins and includes an anchoring region at the NH2 terminus consisting of hydrophobic amino acids, we also constructed deletion **mutants** of NA in this region. Replacement of DNA coding for the first 10 NH2-terminal amino acids with SV40 and linker sequences had no apparent effect on NA expression, glycosylation, transport to the cell surface, or enzymatic activity. However, further deletion of NA DNA encoding the first 26 amino acids abolished NA expression. These data suggest that the hydrophobic NH2-terminal region is multifunctional and is important in biosynthesis and translocation of NA across the membrane as well as in anchoring the protein.

L14 ANSWER 27 OF 29 MEDLINE on STN DUPLICATE 16
ACCESSION NUMBER: 84057638 MEDLINE
DOCUMENT NUMBER: 84057638 PubMed ID: 6196188
TITLE: Effects of lignite fly ash particulates and soluble components on the interferon system.
AUTHOR: Hahon N; Booth J A; Sepulveda M J
SOURCE: ENVIRONMENTAL RESEARCH, (1983 Dec) 32 (2) 329-43.
Journal code: 0147621. ISSN: 0013-9351.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198401
ENTRY DATE: Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19840126

AB Induction of interferon by **influenza** virus was depressed by approximately 50% when **mammalian** (LLC-MK2) **cell** monolayers were pretreated with lignite fly ash. The presence of fly ash, however, did not impair the ability of exogenous interferon to confer antiviral cellular resistance. **Influenza** virus multiplication in cell monolayers pretreated with fly ash attained a twofold higher level of growth than that noted in normal cell monolayers. This was related to suppression of viral interferon induction by fly ash. Whereas aqueous extracts of fly ash had no adverse effect on interferon induction, extractions of fly ash by either polar or nonpolar solvents, by horse serum with or without EDTA (a metal chelator), and fractionation of serum extracts yielded

corresponding compounds, most likely organic and inorganic, that were antagonistic to viral interferon induction. Residual fly ash particulates after extraction by horse serum with EDTA were still capable of inhibiting viral induction of interferon. These findings indicate that several soluble components inherent to lignite fly ash and the particulate matrix per se may modify, independently or in concert, cellular defense behavior. Neither polar, nonpolar, nor horse serum extracts of lignite fly ash, however, showed **mutagenic** activity as determined by the Salmonella histidine reversion assay. Removal of cell-membrane-bound **sialic** acid (**N-acetylneuraminic** acid) by neuraminidase or pretreatment of lignite fly ash with **sialic** acid abolished the adverse activity of fly ash on viral interferon induction. This suggests that the interaction of cell-membrane-bound **sialic** acid residue with fly ash particulates may be involved in the altered state of cellular behavior described in response to viral induction of interferon.

L14 ANSWER 28 OF 29 MEDLINE on STN DUPLICATE 17
ACCESSION NUMBER: 81239727 MEDLINE
DOCUMENT NUMBER: 81239727 PubMed ID: 6265461
TITLE: Glycosylation does not determine segregation of viral envelope proteins in the plasma membrane of epithelial cells.
AUTHOR: Green R F; Meiss H K; Rodriguez-Boulan E
SOURCE: JOURNAL OF CELL BIOLOGY, (1981 May) 89 (2) 230-9. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198109
ENTRY DATE: Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19810915

AB Enveloped viruses are excellent tools for the study of the biogenesis of epithelial polarity, because they bud asymmetrically from confluent monolayers of epithelial cells and because polarized budding is preceded by the accumulation of envelope proteins exclusively in the plasma membrane regions from which the viruses bud. In this work, three different experimental approaches showed that the carbohydrate moieties do not determine the final surface localization of either **influenza** (WSN strain) or vesicular stomatitis virus (VSV) envelope proteins in infected **Madin -Darby Canine** Kidney (**MDCK**) **cells**, as determined by immunofluorescence and immunoelectron microscopy, using ferritin as a marker. Infected concanavalin A- and ricin 1-resistant **mutants** of **MDCK cells**, with alterations in glycosylation, exhibited surface distributions of viral glycoproteins identical to those of the parental **cell** line, i.e., **influenza** envelope proteins were exclusively found in the apical surface, whereas VSV G protein was localized only in the basolateral region. **MDCK cells** treated with tunicamycin, which abolishes the glycosylation of viral glycoproteins, exhibited the same distribution of envelope proteins as control **cells**, after infection with VSF or **influenza**. A temperature-sensitive **mutant** of **influenza** WSN,

ts3, which, when grown at the nonpermissive temperature of 39.5 degrees C, retains the **sialic** acid residues in the envelope glycoproteins, showed, at both 32 degrees C (permissive temperature) and 39.5 degrees C, budding polarity and viral glycoprotein distribution identical to those of the parental WSN strain, when grown in **MDCK cells**. These results demonstrate that carbohydrate moieties are not components of the addressing signals that determine the polarized distribution of viral envelope proteins, and possibly of the intrinsic cellular plasma membrane proteins, in the surface of epithelial cells.

L14 ANSWER 29 OF 29 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 80041761 MEDLINE
DOCUMENT NUMBER: 80041761 PubMed ID: 91354
TITLE: Latex fetuin spheres as probes for **influenza** virus neuraminidase in productively and abortively infected cells.
AUTHOR: Israel A; Niveleau A; Quash G; Richard M H
SOURCE: ARCHIVES OF VIROLOGY, (1979) 61 (3) 183-99. Journal code: 7506870. ISSN: 0304-8608.
PUB. COUNTRY: Austria
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 197912
ENTRY DATE: Entered STN: 19900315
Last Updated on STN: 19980206
Entered Medline: 19791218

AB Fetuin bound latex spheres do not adhere to the membranes of non-infected cells but adhere to those of cells productively infected by fowl plague virus (FPV Dobson strain). In contrast, asialo fetuin spheres do not attach to the membranes of productively infected cells. Moreover latex fetuin spheres incubated with extracts of productively infected cells and extensively washed are specifically enriched in neuraminidase activity without any trace of haemagglutinin. These observations suggest that viral neuraminidase in the membrane is the site of attachment of the **sialic** acid moieties of fetuin spheres. These neuraminidase sites are detectable when L **cells** are productively infected by a **mammalian cell** adapted **mutant** of the Dobson strain (FPV-B) but are not detectable on L **cells** abortively infected by wild type (FPV+). However, even in the abortive system, neuraminidase is synthesised de novo as shown by its labelling with 14C-glucosamine and by its isolation from labelled extracts of infected cells by latex fetuin spheres. These results show that misintegration of viral neuraminidase in the plasma membrane of L cells is a feature of abortive infection of these cells by the Dobson strain of FPV. However the relationship (if any) of this misintegration to abortive infection remains to be established.

(FILE 'MEDLINE' ENTERED AT 15:01:17 ON 18 DEC 2003)
L16 13442 SEA FILE=MEDLINE ABB=ON PLU=ON INFLUENZA/CT
L17 7064 SEA FILE=MEDLINE ABB=ON PLU=ON "SIALIC ACIDS"/CT
L18 221 SEA FILE=MEDLINE ABB=ON PLU=ON L16 AND L17
L19 16678 SEA FILE=MEDLINE ABB=ON PLU=ON MUTAGENESIS/CT
L20 43955 SEA FILE=MEDLINE ABB=ON PLU=ON "POLYMORPHISM (GENETICS)"/CT

L21 165432 SEA FILE=MEDLINE ABB=ON PLU=ON MUTATION/CT
L22 4 SEA FILE=MEDLINE ABB=ON PLU=ON L18 AND (L19 OR L20 OR L21)

L22 ANSWER 1 OF 4 MEDLINE on STN
AN 2001498506 MEDLINE
TI Virology. The origin and control of pandemic influenza.
AU Laver G; Garman E
SO SCIENCE, (2001 Sep 7) 293 (5536) 1776-7.
Journal code: 0404511. ISSN: 0036-8075.

L22 ANSWER 2 OF 4 MEDLINE on STN
AN 2001370297 MEDLINE
TI Position statement: global neuraminidase inhibitor susceptibility network.
AU Zambon M; Hayden F G
SO ANTIVIRAL RESEARCH, (2001 Mar) 49 (3) 147-56. Ref: 30
Journal code: 8109699. ISSN: 0166-3542.

L22 ANSWER 3 OF 4 MEDLINE on STN
AN 1998453440 MEDLINE
TI Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus.
AU Gubareva L V; Matrosovich M N; Brenner M K; Bethell R C; Webster R G
SO JOURNAL OF INFECTIOUS DISEASES, (1998 Nov) 178 (5) 1257-62.
Journal code: 0413675. ISSN: 0022-1899.
AB Zanamivir, a neuraminidase inhibitor, has shown promise as a drug to control influenza. During prolonged treatment with zanamivir, a mutant virus was isolated from an immunocompromised child infected with influenza B virus. A hemagglutinin mutation (198 Thr-->Ile) reduced the virus affinity for receptors found on susceptible human cells. A mutation in the neuraminidase active site (152 Arg-->Lys) led to a 1000-fold reduction in the enzyme sensitivity to zanamivir. When tested in ferrets, the mutant virus had less virulence than the parent; however, it had a growth preference over the parent in zanamivir-treated animals. Despite these changes, the sensitivity of the mutant virus to zanamivir assessed by a standard test in MDCK cells was unaffected. These data indicate that the current methods for monitoring resistant mutants are potentially flawed because no tissue culture system adequately reflects the receptor specificity of human respiratory tract epithelium.

L22 ANSWER 4 OF 4 MEDLINE on STN
AN 1998321153 MEDLINE
TI The interaction of neuraminidase and hemagglutinin mutations in influenza virus in resistance to 4-guanidino-Neu5Ac2en.
AU Blick T J; Sahasrabudhe A; McDonald M; Owens I J; Morley P J; Fenton R J; McKimm-Breschkin J L
SO VIROLOGY, (1998 Jun 20) 246 (1) 95-103.
Journal code: 0110674. ISSN: 0042-6822.
AB We have previously described a 4-guanidino-Neu5Ac2en (zanamivir)-resistant neuraminidase (NA) variant G70C4-G, with an active site mutation Glu 119 to Gly. This variant has been found to also harbor a hemagglutinin (HA) mutation in the receptor binding site, Ser 186 to Phe. Examination of early passages of the G70C4-G virus revealed that this HA mutation had arisen by the first passage. From a subsequent passage two transient variants were isolated which had each acquired a different second HA mutation, Ser

165 to Asn and Lys 222 to Thr. Both were highly drug resistant and drug dependent and their ability to adsorb to and penetrate cells was decreased. Comparison of drug sensitivities between the variant, with the additional HA mutation at Ser 165, and viruses with either mutation alone revealed that these two HA mutations acted synergistically to increase resistance. To determine the contribution to resistance of each of the NA and HA mutations in G70C4-G, the NA mutation was separated from the HA mutation by reassorting. The NA mutation and the HA mutation each conferred low-level resistance to zanamivir, while the two mutations interacted synergistically in the double mutant to give higher resistance in vitro. Infectivity was not adversely affected in the double mutant and while there was a small decrease in sensitivity to zanamivir in the mouse model, there was no detectable resistance to zanamivir in the ferret model.

L16	13442	SEA	FILE=MEDLINE ABB=ON	PLU=ON	INFLUENZA/CT
L19	16678	SEA	FILE=MEDLINE ABB=ON	PLU=ON	MUTAGENESIS/CT
L20	43955	SEA	FILE=MEDLINE ABB=ON	PLU=ON	"POLYMORPHISM (GENETICS)"/CT
L21	165432	SEA	FILE=MEDLINE ABB=ON	PLU=ON	MUTATION/CT
L23	2780	SEA	FILE=MEDLINE ABB=ON	PLU=ON	"N-ACETYLNEURAMINIC ACID"/CT
L24	8	SEA	FILE=MEDLINE ABB=ON	PLU=ON	L16 AND L23
L25	0	SEA	FILE=MEDLINE ABB=ON	PLU=ON	L24 AND (L19 OR L20 OR L21)

(FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, JICST-EPLUS, JAPIO, PHIC, PHIN, TOXCENTER, CABA, AGRICOLA, VETU, VETB' ENTERED AT 15:05:42 ON 18 DEC 2003)

Author

L26	1399	S	"KAWAOKA Y"?/AU
L27	95	S	L4 AND L26
L28	95	S	L27 AND INFLUENZ?
L29	29	DUP	REM L28 (66 DUPLICATES REMOVED)

L29 ANSWER 1 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER:	2003:656882 HCAPLUS
DOCUMENT NUMBER:	139:161823
TITLE:	Signal for packaging of **influenza** virus vectors
INVENTOR(S):	**Kawaoka, Yoshihiro**
PATENT ASSIGNEE(S):	Wisconsin Alumni Research Foundation, USA
SOURCE:	PCT Int. Appl., 110 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003068923	A2	20030821	WO 2003-US4233	20030212

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,

NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM.
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-356538P P 20020213
US 2003-483679P P 20030107

AB The invention provides a packaging (incorporation) signal for **influenza** virus vectors, and methods of using the signal to transmit and maintain **influenza** viral and foreign nucleic acid in virus and cells.

L29 ANSWER 2 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2002:676181 HCAPLUS
DOCUMENT NUMBER: 137:214224
TITLE: Identification of lectin-resistant animal cells with reduced **sialic** acid for **influenza** virus mutant capable of replicating in an altered host cell
INVENTOR(S): **Kawaoka, Yoshihiro**
PATENT ASSIGNEE(S): Wisconsin Alumni Research Foundation, USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002068632	A2	20020906	WO 2002-US5455	20020222
WO 2002068632	A3	20030530		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002197705	A1	20021226	US 2002-81170	20020222
EP 1364006	A2	20031126	EP 2002-724994	20020222

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRIORITY APPLN. INFO.: US 2001-271044P P 20010223
WO 2002-US5455 W 20020222

AB The invention provides an isolated mutant vertebrate cell which has altered expression of **sialic** acid for **influenza** virus, and methods of preparing and using the mutant cell. The invention provides cells useful to propagate **influenza** virus mutants having reduced sialidase activity caused by deletion mutation in NA gene. To produce cell lines with a decreased level of **sialic** acid expression on the cell surface, two lectins

were used, SNA and MAA, to treat the cells. The MDCK cell line, which supports the growth of **influenza** viruses, was used as a parent cell for lectin selection. Viruses lacking sialidase activity can grow efficiently in cells expressing a reduced level of **sialic** acid because the viral glycoproteins are not sialylated extensively compared with those in normal cell lines and are not bound by the HA (hemagglutinin), thus preventing viral aggregation.

L29 ANSWER 3 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2001:832924 HCAPLUS
DOCUMENT NUMBER: 136:66169
TITLE: Amino acids responsible for the absolute sialidase activity of the **influenza** A virus neuraminidase: relationship to growth in the duck intestine
AUTHOR(S): Kobasa, Darwyn; Wells, Krisna; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI, 53706, USA
SOURCE: Journal of Virology (2001), 75(23), 11773-11780
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The 1957 human pandemic strain of **influenza** A virus contained an avian virus hemagglutinin (HA) and neuraminidase (NA), both of which acquired specificity for the human receptor, **N -acetylneuraminic** acid linked to galactose of cellular glycoconjugates via an α2-6 bond (NeuAcα2-6Gal). Although the NA retained considerable specificity for NeuAcα2-3Gal, its original substrate in ducks, it lost the ability to support viral growth in the duck intestine, suggesting a growth-restrictive change other than a shift in substrate specificity. To test this possibility, we generated a panel of reassortant viruses that expressed the NA genes of human H2N2 viruses isolated from 1957 to 1968 with all other genes from the avian virus A/duck/Hong Kong/278/78 (H9N2). Only the NA of A/Singapore/1/57 supported efficient viral growth in the intestines of orally inoculated ducks. The growth-supporting capacity of the NA correlated with a high level of enzymic activity, comparable to that found to be associated with avian virus NAs. The specific activities of the A/Ann Arbor/6/60 and A/England/12/62 NAs, which showed greatly restricted abilities to support viral growth in ducks, were only 8 and 5%, resp., of the NA specific activity for A/Singapore/1/57. Using chimeric constructs based on A/Singapore/1/57 and A/England/12/62 NAs, we localized the determinants of high specific NA activity to a region containing six amino acid substitutions in A/England/12/62: Ser331→Arg, Asp339→Asn, Asn367→Ser, Ser370→Leu, Asn400→Ser, and Pro431→Glu. Five of these six residues (excluding Asn400) were required and sufficient for the full specific activity of the A/Singapore/1/57 NA. Thus, in addition to a change in substrate specificity, a reduction in high specific activity may be required for the adaptation of avian virus NAs to growth in humans. This change is likely needed to maintain an optimal balance between NA activity and the lower affinity shown by

human virus HAs for their cellular receptor.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 4 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2001:240511 HCAPLUS
DOCUMENT NUMBER: 135:18442
TITLE: Adaptation of **influenza** A viruses to cells expressing low levels of **sialic** acid leads to loss of neuraminidase activity
AUTHOR(S): Hughes, Mark T.; McGregor, Martha; Suzuki, Takashi; Suzuki, Yasuo; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI, 53706, USA
SOURCE: Journal of Virology (2001), 75(8), 3766-3770
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Influenza** A viruses possess two virion surface proteins, hemagglutinin (HA) and neuraminidase (NA). The HA binds to sialyloligosaccharide viral receptors, while the NA removes **sialic** acids from the host cell and viral sialyloligosaccharides. Alterations of the HA occur during adaptation of **influenza** viruses to new host species, as in the 1957 and 1968 **influenza** pandemics. To gain a better understanding of the contributions of the HA and possibly the NA to this process, we generated cell lines expressing reduced levels of the **influenza** virus receptor determinant, **sialic** acid, by selecting Madin-Darby canine kidney cells resistant to a lectin specific for **sialic** acid linked to galactose by α(2-3) or α(2-6) linkages. One of these cell lines had less than 1/10 as much **N-acetylneuraminic** acid as its parent cell line. When serially passaged in this cell line, human H3N2 viruses lost sialidase activity due to a large internal deletion in the NA gene, without alteration of the HA gene. These findings indicate that NA mutations can contribute to the adaptation of **influenza** A virus to new host environments and hence may play a role in the transmission of virus across species.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 5 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2001:205125 HCAPLUS
DOCUMENT NUMBER: 134:363759
TITLE: **Sialic** acid species as a determinant of the host range of **influenza** A viruses
AUTHOR(S): Suzuki, Yasuo; Ito, Toshihiro; Suzuki, Takashi; Holland, Robert E., Jr.; Chambers, Thomas M.; Kiso, Makoto; Ishida, Hideharu; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: Department of Biochemistry, School of Pharmaceutical Sciences, University of Shizuoka,

Shizuoka, 422-8526, Japan
SOURCE: Journal of Virology (2000), 74(24), 11825-11831
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The distribution of **sialic** acid (SA) species varies among animal species, but the biol. role of this variation is largely unknown. **Influenza** viruses differ in their ability to recognize SA-galactose (Gal) linkages, depending on the animal hosts from which they are isolated. For example, human viruses preferentially recognize SA linked to Gal by the α2,6(SAα2,6Gal) linkage, while equine viruses favor SAα2,3Gal. However, whether a difference in relative abundance of specific SA species (**N-acetylneuraminic** acid [NeuAc] and **N-glycolylneuraminic** acid [**NeuGc**]) among different animals affects the replicative potential of **influenza** viruses is uncertain. We therefore examined the requirement for the hemagglutinin (HA) for support of viral replication in horses, using viruses whose HAs differ in receptor specificity. A virus with an HA recognizing NeuAcα2,6Gal but not NeuAcα2,3Gal or **NeuGc**.alpha.2,3Gal or **NeuGc**.alpha.2,3Gal failed to replicate in horses, while one with an HA recognizing the **NeuGc**.alpha.2,3Gal moiety replicated in horses. Furthermore, biochem. and immunohistochem. analyses and a lectin-binding assay demonstrated the abundance of the **NeuGc** α2,3Gal moiety in epithelial cells of horse trachea, indicating that recognition of this moiety is critical for viral replication in horses. Thus, these results provide evidence of a biol. effect of different SA species in different animals.
REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 6 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2000:678571 HCAPLUS
DOCUMENT NUMBER: 133:332449
TITLE: Recognition of **N-glycolylneuraminic** acid linked to galactose by the α2,3 linkage is associated with intestinal replication of **influenza** A virus in ducks
AUTHOR(S): Ito, Toshihiro; Suzuki, Yasuo; Suzuki, Takashi; Takada, Ayato; Horimoto, Taisuke; Wells, Krisna; Kida, Hiroshi; Otsuki, Koichi; Kiso, Makoto; Ishida, Hideharu; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: Department of Veterinary Public Health, Faculty of Agriculture, Tottori University, Tottori, 680-8553, Japan
SOURCE: Journal of Virology (2000), 74(19), 9300-9305
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The hemagglutinin (HA) of H3 human **influenza** viruses does not support viral replication in duck intestine despite its avian origin. A Leu-to-Gln mutation at position 226 and a Ser-to-Gly

mutation at position 228 in the HA of human A/Udorn/307/72 (H3N2) permit a reassortant virus [human Udorn HA, with all other genes from A/mallard/New York/6750/78 (H2N2)] to replicate in ducks. To understand the mol. basis of this change in host range restriction, the authors investigated the receptor specificity of duck **influenza** viruses as well as of human-duck virus reassortants. The results indicate that the recognition of a glycoconjugate moiety possessing **N-glycolylneuraminic** acid (**NeuGc**) linked to galactose by the α2,3 linkage (**NeuGc**.alpha.2,3Gal) is associated with viral replication in duck intestine. Immunofluorescence assays with **NeuGc**.alpha.2,3Gal-specific antiserum detected this moiety primarily on the crypt epithelial cells of duck colon. Such recognition, together with biochem. evidence of **NeuGc** in crypt cells, correlated exactly with the ability of the virus to replicate in duck colon. These results suggest that recognition of the **NeuGc**.alpha.2,3-Gal moiety plays an important role in the enterotropism of avian **influenza** viruses.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 7 OF 29 MEDLINE on STN DUPLICATE 6

ACCESSION NUMBER: 2000459404 MEDLINE
DOCUMENT NUMBER: 20411424 PubMed ID: 10954551
TITLE: Early alterations of the receptor-binding properties of H1, H2, and H3 avian **influenza** virus hemagglutinins after their introduction into mammals.
AUTHOR: Matrosovich M; Tuzikov A; Bovin N; Gambaryan A; Klimov A; Castrucci M R; Donatelli I; **Kawaoka Y**
CORPORATE SOURCE: Department of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, Russia.. Mikhail.Mastrosovich@stjude.org
CONTRACT NUMBER: CA-21765 (NCI)
SOURCE: JOURNAL OF VIROLOGY, (2000 Sep) 74 (18) 8502-12. Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200009
ENTRY DATE: Entered STN: 20001005
Last Updated on STN: 20001005
Entered Medline: 20000927

AB Interspecies transmission of **influenza** A viruses circulating in wild aquatic birds occasionally results in **influenza** outbreaks in mammals, including humans. To identify early changes in the receptor binding properties of the avian virus hemagglutinin (HA) after interspecies transmission and to determine the amino acid substitutions responsible for these alterations, we studied the HAs of the initial isolates from the human pandemics of 1957 (H2N2) and 1968 (H3N2), the European swine epizootic of 1979 (H1N1), and the seal epizootic of 1992 (H3N3), all of which were caused by the introduction of avian virus HAs into these species. The viruses were assayed for their ability to bind the synthetic sialylglycopolymers 3'SL-PAA and 6'SLN-PAA, which

contained, respectively, 3'-sialyllactose (the receptor determinant preferentially recognized by avian **influenza** viruses) and 6'-sialyl(N-acetyllactosamine) (the receptor determinant for human viruses). Avian and seal viruses bound 6'SLN-PAA very weakly, whereas the earliest available human and swine epidemic viruses bound this polymer with a higher affinity. For the H2 and H3 strains, a single mutation, 226Q-->L, increased binding to 6'SLN-PAA, while among H1 swine viruses, the 190E-->D and 225G-->E mutations in the HA appeared important for the increased affinity of the viruses for 6'SLN-PAA. Amino acid substitutions at positions 190 and 225 with respect to the avian virus consensus sequence are also present in H1 human viruses, including those that circulated in 1918, suggesting that substitutions at these positions are important for the generation of H1 human pandemic strains. These results show that the receptor-binding specificity of the HA is altered early after the transmission of an avian virus to humans and pigs and, therefore, may be a prerequisite for the highly effective replication and spread which characterize epidemic strains.

L29 ANSWER 8 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2000:423184 HCAPLUS
DOCUMENT NUMBER: 133:174422
TITLE: Balanced hemagglutinin and neuraminidase activities are critical for efficient replication of **influenza** A virus
AUTHOR(S): Mitnaul, Lyndon J.; Matrosovich, Mikhail N.; Castrucci, Maria R.; Tuzikov, Alexander B.; Bovin, Nikolai V.; Kobasa, Darwyn; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: Department of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis, TN, 38101, USA
SOURCE: Journal of Virology (2000), 74(13), 6015-6020
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The SD0 mutant of **influenza** virus A/WSN/33 (WSN), characterized by a 24-amino-acid deletion in the neuraminidase (NA) stalk, does not grow in embryonated chicken eggs because of defective NA function. Continuous passage of SD0 in eggs yielded 10 independent clones that replicated efficiently. Characterization of these egg-adapted viruses showed that five of the viruses contained insertions in the NA gene from the PB1, PB2, or NP gene, in the region linking the transmembrane and catalytic head domains, demonstrating that recombination of **influenza** viral RNA segments occurs relatively frequently. The other five viruses did not contain insertions in this region but displayed decreased binding affinity toward sialylglycoconjugates, compared with the binding properties of the parental virus. Sequence anal. of one of the latter viruses revealed mutations in the hemagglutinin (HA) gene, at sites in close proximity to the **sialic** acid receptor-binding pocket. These mutations appear to compensate for reduced NA function due to stalk deletions. Thus, balanced HA-NA functions are necessary for efficient **influenza** virus replication.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE

IN THE RE FORMAT

L29 ANSWER 9 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2000:346403 HCAPLUS
DOCUMENT NUMBER: 133:71351
TITLE: **Influenza** A viruses lacking sialidase activity can undergo multiple cycles of replication in cell culture, eggs, or mice
AUTHOR(S): Hughes, Mark T.; Matrosovich, Mikhail; Rodgers, M. Elizabeth; McGregor, Martha; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, WI, 53706, USA
SOURCE: Journal of Virology (2000), 74(11), 5206-5212
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Influenza** A viruses possess both hemagglutinin (HA), which is responsible for binding to the terminal **sialic** acid of sialyloligosaccharides on the cell surface, and neuraminidase (NA), which contains sialidase activity that removes **sialic** acid from sialyloligosaccharides. Interplay between HA receptor-binding and NA receptor-destroying sialidase activity appears to be important for replication of the virus. Previous studies by others have shown that **influenza** A viruses lacking sialidase activity can undergo multiple cycles of replication if sialidase activity is provided exogenously. To investigate the sialidase requirement of **influenza** viruses further, we generated a series of sialidase-deficient mutants. Although their growth was less efficient than that of the parental NA-dependent virus, these viruses underwent multiple cycles of replication in cell culture, eggs, and mice. To understand the mol. basis of this viral growth adaptation in the absence of sialidase activity, the authors investigated changes in the HA receptor-binding affinity of the sialidase-deficient mutants. The results show that mutations around the HA receptor-binding pocket reduce the virus's affinity for cellular receptors, compensating for the loss of sialidase. Thus, sialidase activity is not absolutely required in the **influenza** A virus life cycle but appears to be necessary for efficient virus replication.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 10 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 1999:456484 HCAPLUS
DOCUMENT NUMBER: 131:239673
TITLE: Amino acid residues contributing to the substrate specificity of the **influenza** A virus neuraminidase
AUTHOR(S): Kobasa, Darwyn; Kodihalli, Shantha; Luo, Ming; Castrucci, Maria R.; Donatelli, Isabella; Suzuki, Yasuo; Suzuki, Takashi; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: Department of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis,

TN, 38101, USA
SOURCE: Journal of Virology (1999), 73(8), 6743-6751
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Influenza** A viruses possess two glycoprotein spikes on the virion surface: hemagglutinin (HA), which binds to oligosaccharides containing terminal **sialic** acid, and neuraminidase (NA), which removes terminal **sialic** acid from oligosaccharides. Hence, the interplay between these receptor-binding and receptor-destroying functions assumes major importance in viral replication. In contrast to the well-characterized role of HA in host range restriction of **influenza** viruses, there is only limited information on the role of NA substrate specificity in viral replication among different animal species. We therefore investigated the substrate specificities of NA for linkages between N-acetyl **sialic** acid and galactose (NeuAcα2-3Gal and NeuAcα2-6Gal) and for different mol. species of **sialic** acids (N-acetyl and N-glycolyl **sialic** acids) in **influenza** A viruses isolated from human, avian, and pig hosts. Substrate specificity assays showed that all viruses had similar specificities for NeuAcα2-3Gal, while the activities for NeuAcα2-6Gal ranged from marginal, as represented by avian and early N2 human viruses, to high (although only one-third the activity for NeuAcα2-3Gal), as represented by swine and more recent N2 human viruses. Using site-specific mutagenesis, we identified in the earliest human virus with a detectable increase in NeuAcα2-6Gal specificity a change at position 275 (from isoleucine to valine) that enhanced the specificity for this substrate. Valine at position 275 was maintained in all later human viruses as well as swine viruses. A similar examination of **N-glycolylneuraminic** acid (**NeuGc**) specificity showed that avian viruses and most human viruses had low to moderate activity for this substrate, with the exception of most human viruses isolated between 1967 and 1969, whose **NeuGc** specificity was as high as that of swine viruses. The amino acid at position 431 was found to determine the level of **NeuGc** specificity of NA: lysine conferred high **NeuGc** specificity, while proline, glutamine, and glutamic acid were associated with lower **NeuGc** specificity. Both residues 275 and 431 lie close to the enzymic active site but are not directly involved in the reaction mechanism. This finding suggests that the adaptation of NA to different substrates occurs by a mechanism of amino acid substitutions that subtly alter the conformation of NA in and around the active site to facilitate the binding of different species of **sialic** acid.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 11 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 1999:807034 HCAPLUS
DOCUMENT NUMBER: 132:177974
TITLE: Substitution of amino acid residue in **influenza** A virus hemagglutinin affects recognition of sialyl-oligosaccharides containing **N-**

glycolylneuraminic acid
AUTHOR(S): Masuda, H.; Suzuki, T.; Sugiyama, Y.; Horiike, G.; Murakami, K.; Miyamoto, D.; Jwa Hidari, K. I.-P.; Ito, T.; Kida, H.; Kiso, M.; Fukunaga, K.; Ohuchi, M.; Toyoda, T.; Ishihama, A.; **Kawaoka, Y.**; Suzuki, Y.
CORPORATE SOURCE: Department of Biochemistry, School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka, Japan
SOURCE: FEBS Letters (1999), 464(1,2), 71-74
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Sialic** acids are essential components of cell surface receptors used by **influenza** viruses. To determine the mol. mechanisms of viral recognition of two major species of **sialic** acids, **N-acetylneuraminic** acid (Neu5Ac) and **N-glycolylneuraminic** acid (Neu5Gc), we tested the binding reactivity of nine human H3 **influenza** A viruses to sialylglycolipids containing type II sugar chain and different mol. species of terminal **sialic** acids. All human H3 viruses tested except A/Memphis/1/71 bound both Neu5Ac and Neu5Gc. Nucleotide sequence anal. suggests that amino acids at 143, 155, and 158 are linked to the viral recognition of Neu5Gc.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 12 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 11
ACCESSION NUMBER: 1998:463992 HCAPLUS
DOCUMENT NUMBER: 129:186627
TITLE: Molecular mechanisms of serum resistance of human **influenza** H3N2 virus and their involvement in virus adaptation in a new host
AUTHOR(S): Matrosovich, Mikhail; Gao, Peng; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: M. P. Chumakov Institute of Poliomyelitis and Viral Encephalitides, Moscow, 142 782, Russia
SOURCE: Journal of Virology (1998), 72(8), 6373-6380
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB H3N2 human **influenza** viruses that are resistant to horse, pig, or rabbit serum possess unique amino acid mutations in their hemagglutinin (HA) protein. To determine the mol. mechanisms of this resistance, the authors characterized the receptor-binding properties of these mutants by measuring their affinity for total serum protein inhibitors and for soluble receptor analogs. Pig serum-resistant variants displayed a markedly decreased affinity for total pig serum sialylglycoproteins (which contain predominantly 2-6 linkage between **sialic** acid and galactose residues) and for the sialyloligosaccharide 6→-sialyl(N-acetyllactosamine). These properties correlated with the substitution 186S→I in HA1. The major inhibitory activity in rabbit serum was found to be a β inhibitor with characteristics of mannose-binding lectins. Rabbit serum-resistant variants exhibited decreased sensitivity to

this inhibitor due to the loss of a glycosylation sequon at positions 246 to 248 of the HA. In addition to a somewhat reduced affinity for 6'-sialyl(N-acetyllactosamine)-containing receptors, horse serum-resistant variants lost the ability to bind the viral neuraminidase-resistant 4-O-acetylated **sialic** acid moieties of equine α2-macroglobulin because of the mutation 145N→K/D in their HA1. These results indicate that **influenza** viruses become resistant to serum inhibitors because their affinity for these inhibitors is reduced. To determine whether natural inhibitors play a role in viral evolution during interspecies transmission, we compared the receptor-binding properties of H3N8 avian and equine viruses, including two strains isolated during the 1989 to 1990 equine **influenza** outbreak, which was caused by an avian virus in China. Avian strains bound 4-O-acetylated **sialic** acid residues of equine α2-macroglobulin, whereas equine strains did not. The earliest avian-like isolate from a horse **influenza** outbreak bound to this **sialic** acid with an affinity similar to that of avian viruses; a later isolate, however, displayed binding properties more similar to those of classical equine strains. These data suggest that the neuraminidase-resistant sialylglycoconjugates present in horses exert selective pressure on the receptor-binding properties of avian virus HA after its introduction into this host.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 13 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 12
ACCESSION NUMBER: 1998:568471 HCAPLUS
DOCUMENT NUMBER: 130:23542
TITLE: Changes in H3 **influenza** A virus receptor specificity during replication in humans
AUTHOR(S): Ryan-Poirier, Kathleen; Suzuki, Yasuo; Bean, William J.; Kobasa, Darwyn; Takada, Ayato; Ito, Toshihiro; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: Department of a Virology and Molecular Biology, St. Jude Children's Research Hospita, Memphis, TN, 38105, USA
SOURCE: Virus Research (1998), 56(2), 169-176
CODEN: VIREDF; ISSN: 0168-1702
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Influenza** A viruses of the H3 subtype caused the 1968 Hong Kong pandemic, the hemagglutinin (HA) gene being introduced into humans following a reassortment event with an avian virus. Receptor specificity and serum inhibitor sensitivity of the HA of **influenza** A viruses are linked to the host species. Human H3 viruses preferentially recognize N-acetyl **sialic** acid linked to galactose by α2,6 linkages (Neu5Acα2,6Gal) and are sensitive to serum inhibitors, whereas avian and equine viruses preferentially recognize Neu5Acα2,3Gal linkages and are resistant to serum inhibitors. The authors have examined the receptor specificity and serum inhibitor sensitivity of H3 human **influenza** A viruses from the time they were introduced into the human population to gain insight into the mechanism of viral

mol. evolution and host tropism. All of the viruses were sensitive to neutralization and hemagglutination inhibition by horse serum. Early H3 viruses were resistant to pig and rabbit serum inhibitors. Viruses isolated after 1977 were uniformly sensitive to inhibition by pig and rabbit sera. The recognition of Neu5Acα2,3Gal or Neu5Acα2,6Gal linkages was not correlated with the serum sensitivity. These data showed that the receptor specificity of HA, measured as inhibitor sensitivity, has changed during replication in humans since its introduction from an avian virus.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 14 OF 29 MEDLINE on STN DUPLICATE 13
ACCESSION NUMBER: 97404682 MEDLINE
DOCUMENT NUMBER: 97404682 PubMed ID: 9261394
TITLE: Neuraminidase hemadsorption activity, conserved in avian **influenza** A viruses, does not influence viral replication in ducks.
AUTHOR: Kobasa D; Rodgers M E; Wells K; **Kawaoka Y**
CORPORATE SOURCE: Department of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis, Tennessee 38101, USA.
CONTRACT NUMBER: AI33898 (NIAID)
CA-21765 (NCI)
SOURCE: JOURNAL OF VIROLOGY, (1997 Sep) 71 (9) 6706-13.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 19970926
Last Updated on STN: 19990129
Entered Medline: 19970917

AB The N1 and N9 neuraminidase (NA) subtypes of **influenza** A viruses exhibit significant hemadsorption activity that localizes to a site distinct from that of the enzymatic active site. To determine the conservation of hemadsorption activity among different NAs, we have examined most of the NA subtypes from avian, swine, equine, and human virus isolates. All subtypes of avian virus NAs examined and one equine virus N8 NA possessed high levels of hemadsorption activity. A swine virus N1 NA exhibited only weak hemadsorption activity, while in human virus N1 and N2 NAs, the activity was detected at a much lower level than in avian virus NAs. NAs which possessed hemadsorption activity for chicken erythrocytes (RBCs) were similarly able to adsorb human RBCs. However, none of the hemadsorption-positive NAs could bind equine, swine, or bovine RBCs, suggesting that RBCs from these species lack molecules, recognized by the NA hemadsorption site, present on human and chicken RBCs. Mutagenesis of the putative hemadsorption site of A/duck/Hong Kong/7/75 N2 NA abolished the high level of hemadsorption activity exhibited by the wild-type protein but also resulted in a 50% reduction of the NA enzymatic activity. A transfectant virus, generated by reverse genetics, containing this mutated NA replicated 10-fold less efficiently in chicken embryo fibroblast cultures than did a transfectant virus expressing the wild-type NA. However, both viruses replicated equally well in

Peking ducks. Although conservation of NA hemadsorption activity among avian virus NAs suggests the maintenance of a required function of NA, loss of the activity does not preclude the replication of the virus in an avian host.

L29 ANSWER 15 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 14
ACCESSION NUMBER: 1997:185285 HCAPLUS
DOCUMENT NUMBER: 126:274582
TITLE: Differences in **sialic** acid-galactose linkages in the chicken egg amnion and allantois influence human **influenza** virus receptor specificity and variant selection
AUTHOR(S): Ito, Toshihiro; Suzuki, Yasuo; Takada, Ayato; Kawamoto, Ayumi; Otsuki, Koichi; Masuda, Hiroyuki; Yamada, Mika; Suzuki, Takashi; Kida, Hiroshi; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: Dep. Disease Control, Grad. Sch. Vet. Med., Sapporo, 060, Japan
SOURCE: Journal of Virology (1997), 71(4), 3357-3362
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human **influenza** viruses are more efficiently isolated by inoculating patient samples into the amniotic rather than the allantoic cavity of embryonated chicken eggs. This type of cultivation selects virus variants with mutations around the hemagglutinin (HA) receptor binding site. To understand the mol. basis of these phenomena, the abundances of **sialic** acid (SA) linked to galactose (Gal) by the α-2,3 linkage (SAα2,3Gal) and SAαa2,6Gal in egg amniotic and allantoic cells and in Madin-Darby canine kidney (MDCK) cells was investigated. Using SA-Gal linkage-specific lectins (Maackia amurensis agglutinin specific for SAα2,6Gal and Sambucus nigra agglutinin specific for SAα2,3Gal), SAα2,3Gal was found in both allantoic and amniotic cells and SAα2,6Gal in only the amniotic cells. MDCK cells contained both linkages. To investigate how this difference in abundances of SAα2,3Gal and SAα2,6Gal in allantoic and amniotic cells affects the appearance of host cell variants in eggs, the receptor specificities and HA amino acid sequences of 2 different patient viruses which were isolated and passaged in the amnion or in the allantois and were determined and compared with MDCK cell-grown viruses. The viruses maintained high SAα2,6Gal specificities when grown in MDCK cells or following ≤2 amniotic passages; however, further passages in either the amnion or allantois resulted in the acquisition of, or a complete shift to, SAα2,3Gal specificity, depending on the virus strain. This change in receptor specificity was accompanied by the appearance of variants in the population with Leu-to-Gln mutations at position 226 in their HA. These findings suggest that lack of SAα2,6Gal linkages in the allantois of chicken eggs is a selective pressure for the appearance of host cell variants with altered receptor specificities and amino acid changes at position 226.

L29 ANSWER 16 OF 29 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1997:422695 BIOSIS

DOCUMENT NUMBER: PREV199799721898
TITLE: Sialyl-linkage mediated selection for the appearance of host cell variants of **influenza** A viruses.
AUTHOR(S): Suzuki, Yusuo [Reprint author]; Ito, Toshihiro; Masuda, Hiroyuki [Reprint author]; Takada, Ayato; Kawamoto, Ayumi; Otsuki, Koichi; Miyamoto, Daisei [Reprint author]; Suzuki, Takashi [Reprint author]; Kida, Hiroshi; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: Dep. Biochem., Univ. Shizuoka Sch. Pharm. Sci., Shizuoka, Japan
SOURCE: FASEB Journal, (1997) Vol. 11, No. 9, pp. A1443. Meeting Info.: 17th International Congress of Biochemistry and Molecular Biology in conjunction with the Annual Meeting of the American Society for Biochemistry and Molecular Biology. San Francisco, California, USA. August 24-29, 1997. CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Oct 1997
Last Updated on STN: 8 Oct 1997

L29 ANSWER 17 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 15
ACCESSION NUMBER: 1997:92075 HCAPLUS
DOCUMENT NUMBER: 126:142744
TITLE: Receptor specificity of **influenza** A viruses correlates with the agglutination of erythrocytes from different animal species
AUTHOR(S): Ito, Toshihiro; Suzuki, Yasuo; Mitnaul, Lyndon; Vines, Angela; Kida, Hiroshi; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: Laboratory of Microbiology, Department of Disease Control, Graduate School of Veterinary Medicine, Hokkaido University, Sapporo, 060, Japan
SOURCE: Virology (1997), 227(2), 493-499
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Despite their uniform ability to bind to oligosaccharide-containing terminal **sialic** acids, **influenza** A viruses show differences in receptor specificity. To test whether agglutination of erythrocytes from different animal species could be used to assess the receptor specificity of **influenza** A viruses, the authors determined the agglutinating activities of a range of virus strains, including those with known receptor specificities, using erythrocytes from seven animal species. All equine and avian viruses, including those known to recognize N-acetyl and N-glycolyl **sialic** acid linked to galactose by the α2,3 linkage (NeuAcα2,3Gal and **NeuGc**.alpha.2,3Gal), agglutinated erythrocytes from all of the animal species tested (chickens, ducks, guinea pigs, humans, sheep, horses, and cows). The human viruses, including those known to preferentially recognize NeuAcα2,6Gal, agglutinated all but the horse and cow erythrocytes. Fluorescence-activated cell sorting anal. of

erythrocytes using linkage-specific lectins [Sambucus nigra agglutinin for **sialic** acid (SA)α2,6Gal and Maackia amurensis agglutinin for SAα2,3Gal] showed that both cow and horse erythrocytes contain a large amount of SAα2,3Gal-, but virtually no SA2,6Gal-specific lectin-reactive oligosaccharides on the cell surface, while human and chicken erythrocytes contained both types of oligosaccharides. Considering that the majority (>93%) of **sialic** acid in horse and cow erythrocytes is of the N-glycolyl type, the authors' results suggest that viruses able to agglutinate these erythrocytes (i.e., avian and equine viruses) recognize **NeuGc**.alpha.2,3Gal. These findings also show that agglutinating assays with erythrocytes from different animal species would be useful in characterizing the receptor specificity of **influenza** A viruses.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 18 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 16

ACCESSION NUMBER: 1997:793572 HCAPLUS

DOCUMENT NUMBER: 128:97356

TITLE: Mutations affecting the sensitivity of the **influenza** virus neuraminidase to 4-guanidino-2,4-dideoxy-2,3-dehydro-**N-acetylneuraminic** acid

AUTHOR(S): Goto, Hideo; Bethell, Richard C.; **Kawaoka, Yoshihiro**

CORPORATE SOURCE: Department of Virology and Molecular Biology, St. Jude Children's Research Hospital, Memphis, TN, 38101, USA

SOURCE: Virology (1997), 238(2), 265-272
CODEN: VIRLAX; ISSN: 0042-6822

PUBLISHER: Academic Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB 4-Guanidino-2,4-dideoxy-2,3-dehydro-**N-acetylneuraminic** acid (4-guanidino-Neu5Ac2en) specifically inhibits the **influenza** virus neuraminidase (NA) through interaction of the guanidino group with conserved Glu 119 and Glu 227 residues in the substrate binding pocket of the enzyme. To understand the mechanism by which **influenza** viruses become resistant to 4-guanidino-Neu5Ac2en, we investigated mutations at amino acid residues 119 and 227 in the **influenza** virus NA for their effects on this compound and on NA activity. The NA gene was cloned from the NWS-G70c virus, and mutations were introduced at the codon for amino acid residue 119 or 227. All of the 13 mutants containing a change at residue 119 were transported to the cell surface, although their expression levels ranged from 68.2 to 91.3% of wild type. Mutant NAs that retained at least 20% of the wild-type enzymic activity were tested for their sensitivity to 4-guanidino-Neu5Ac2en and sevenfold less sensitive to this compound than was the wild-type NA. By contrast, only 6 of 13 mutants defined by modifications at residue 227 were transported to the cell surface, and those NAs lacked substantial enzymic activity (9% of wild type, at most). These results suggest that only a limited number of resistant viruses arise through mutations at Glu 119 and Glu 227 under selective pressure from 4-guanidino-Neu5Ac2en and that the development of compds. which interact with 227 Glu more strongly

than does 4-guanidino-Neu5Ac2en may reduce the likelihood of drug-resistant viruses still further.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 19 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 17
ACCESSION NUMBER: 1997:156739 HCAPLUS
DOCUMENT NUMBER: 126:262537
TITLE: Swine **influenza** virus strains recognize sialylsugar chains containing the molecular species of **sialic** acid predominantly present in the swine tracheal epithelium
AUTHOR(S): Suzuki, Takashi; Horiike, Goh; Yamazaki, Yasuhiro; Kawabe, Kaoru; Masuda, Hiroyuki; Miyamoto, Daisei; Matsuda, Masao; Nishimura, Shin-Ichiro; Yamagata, Tatsuya; Ito, Toshihiro; Kida, Hiroshi; **Kawaoka, Yoshihiro**; Suzuki, Yasuo
CORPORATE SOURCE: Department of Biochemistry, University of Shizuoka, School of Pharmaceutical Science, 52-1 Yada, Shizuoka-shi, 422, Japan
SOURCE: FEBS Letters (1997), 404(2,3), 192-196
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors determined the ratio of **N-glycolylneuraminic** acid (Neu5Gc) to **N-acetylneuraminic** acid (Neu5Ac) in swine respiratory epithelia by fluorometric high-performance liquid chromatog., and examined the binding specificity of swine **influenza** virus strains for gangliosides containing different mol. species of **sialic** acid (Neu5Ac and Neu5Gc), and for bovine erythrocyte sialoglycoprotein 2 (GP-2) containing Neu5Gc as its predominate **sialic** acid (96% of total **sialic** acids). The presence of Neu5Gc, which had not been detected in human tracheal epithelia, and Neu5Ac in swine tracheal epithelia was observed in a 1:1 ratio. The swine **influenza** virus H1 and H3 isolates tested, except for A/swine/Iowa/15/30 (H1N1), displayed a marked binding ability for sialylsugar chains containing Neu5Gc compared with that of the human **influenza** virus strains. These results suggest that swine **influenza** viruses recognize sialylsugar chains containing the mol. species of **sialic** acid present predominantly in the swine tracheal epithelium.

L29 ANSWER 20 OF 29 JICST-EPlus COPYRIGHT 2003 JST on STN
ACCESSION NUMBER: 980748788 JICST-EPlus
TITLE: Correlation of the combination specificity of **sialic** acid molecular species existing in a host cell and equine **influenza** virus type A for sialoglyco chain.
AUTHOR: MASUDA HIROYUKI; SUZUKI TAKASHI; HORIIKE TAKESHI; YAMAZAKI YASUHIRO
KIDA HIROSHI
ITO TOSHIHIRO
KISO MAKOTO; HASEGAWA AKIRA

KAWAOKA YOSHIHIRO
CORPORATE SOURCE: Univ. of Shizuoka, Sch. of Pharm. Sci.
Hokkaido Univ., Fac. of Vet. Med.
Tottori Univ., Fac. of Agric.
Gifu Univ., Fac. of Agric.
St.Jude Children's reseach hospital
SOURCE: Nippon Yakugakkai Nenkai Koen Yoshishu, (1997) vol. 117th, no. 3, pp. 124. Journal Code: L0914A
ISSN: 0918-9823
PUB. COUNTRY: Japan
LANGUAGE: Japanese
STATUS: New

L29 ANSWER 21 OF 29 JICST-EPlus COPYRIGHT 2003 JST on STN
ACCESSION NUMBER: 980206805 JICST-EPlus
TITLE: Receptor specificity of an **influenza** virus. **Sialic** acid recognition and breeding in the trachea of a horse.
AUTHOR: ITO TOSHIHIRO; OTSUKI KOICHI
KAWAOKA YOSHIHIRO
KIDA HIROSHI
CORPORATE SOURCE: Tottori Univ.
Uisukonshindai
Hokkaido Univ.
SOURCE: Nippon Jui Gakkai Koen Yoshishu, (1997) vol. 124th, pp. 72. Journal Code: Z0670A
PUB. COUNTRY: Japan
LANGUAGE: Japanese
STATUS: New

L29 ANSWER 22 OF 29 MEDLINE on STN DUPLICATE 18
ACCESSION NUMBER: 96404883 MEDLINE
DOCUMENT NUMBER: 96404883 PubMed ID: 8809024
TITLE: Sulphatide binds to human and animal **influenza** A viruses, and inhibits the viral infection.
AUTHOR: Suzuki T; Sometani A; Yamazaki Y; Horiike G; Mizutani Y; Masuda H; Yamada M; Tahara H; Xu G; Miyamoto D; Oku N; Okada S; Kiso M; Hasegawa A; Ito T; **Kawaoka Y**; Suzuki Y
CORPORATE SOURCE: Department of Biochemistry, University of Shizuoka, School of Pharmaceutical Science, Japan.
SOURCE: BIOCHEMICAL JOURNAL, (1996 Sep 1) 318 (Pt 2) 389-93. Journal code: 2984726R. ISSN: 0264-6021.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19990129
Entered Medline: 19961113

AB We found, by using a virus overlay assay, that **influenza** A virus isolates bind to sulphatide (HSO3-Gal beta 1-->1'Cer), which has no **sialic** acid residue, and that the infection of Madin-Darby canine kidney cells with the human **influenza** virus A/Memphis/1/71 (H3N2) is inhibited by sulphatide. A/Memphis/1/71 (H3N2) causes obvious haemagglutination and low-pH

haemolysis of asialoerythrocytes reconstituted with sulphatide. All **influenza** A virus isolates from the species of animals so far tested bound to sulphatide. The sulphatide-binding specificity of the isolates was different from the viral sialyl-linkage specificity. **Influenza** A virus isolates also bound to galactosyl ceramide (GalCer; Gal beta 1-->1'Cer), as well as sulphatide, in the virus overlay assays. In contrast, the **influenza** virus did not bind to N-deacyl, a derivative of sulphatide, glucosyl ceramide or the other neutral glycolipids tested. These results indicate that the linkage of galactose, or sulphated galactose, to ceramide is important for viral binding.

L29 ANSWER 23 OF 29 JICST-EPlus COPYRIGHT 2003 JST on STN
ACCESSION NUMBER: 960530220 JICST-EPlus
TITLE: **Sialic** acid recognition specificity of **influenza** A virus and **sialic** acid composition of host mucosal epidermal cells.
AUTHOR: SUZUKI TAKASHI; HORIIKE TSUYOSHI; MIYAMOTO HIROMASA; SUZUKI YASUO
KISO MAKOTO; HASEGAWA AKIRA
ITO HIROYOSHI; YOSHIDA HIROSHI
KAWAOKA YOSHIHIRO
CORPORATE SOURCE: Univ. of Shizuoka, Sch. of Pharm. Sci.
Gifu Univ., Fac. of Agric.
Hokkaido Univ., Fac. of Vet. Med.
St. Jude Children's Res. Hospital
SOURCE: Shishitsu Seikagaku Kenkyu (Proceedings of Japanese Conference on the Biochemistry of Lipids), (1996) vol. 38, pp. 175-178. Journal Code: S0461B (Fig. 2, Ref. 10)
ISSN: 0285-1520
PUB. COUNTRY: Japan
DOCUMENT TYPE: Conference; Article
LANGUAGE: Japanese
STATUS: New

L29 ANSWER 24 OF 29 JICST-EPlus COPYRIGHT 2003 JST on STN
ACCESSION NUMBER: 970252864 JICST-EPlus
TITLE: Bonding of glycolipid containing no **sialic** acid to **influenza** A virus.
AUTHOR: SUZUKI TAKASHI; MIYAMOTO TAISEI; OKU NAOTO; OKADA SHOJI; SUZUKI YASUO
KISO MAKOTO; HASEGAWA AKIRA
ITO TOSHIHIRO; **KAWAOKA YOSHIHIRO**
CORPORATE SOURCE: Univ. of Shizuoka, Sch. of Pharm. Sci.
Gifu Univ., Fac. of Agric.
St. Jude Hospital
SOURCE: Nippon Bunshi Seibutsu Gakkai Nenkai Puroguramu, Koen Yoshishu, (1996) vol. 19th, pp. 92. Journal Code: L1278A
PUB. COUNTRY: Japan
LANGUAGE: Japanese
STATUS: New

L29 ANSWER 25 OF 29 JICST-EPlus COPYRIGHT 2003 JST on STN
ACCESSION NUMBER: 970252861 JICST-EPlus
TITLE: Binding specificity of **influenza** A virus to **sialic** acid molecular species and

sialic acid composition of host mucosa epidermal cell.

AUTHOR: HORIIKE TAKESHI; SUZUKI TAKASHI; MASUDA HIROYUKI; SUZUKI YASUO
KISO MAKOTO; HASEGAWA AKIRA
ITO TOSHIHIRO; KIDA HIROSHI
KAWAOKA YOSHIHIRO

CORPORATE SOURCE: Univ. of Shizuoka, Sch. of Pharm. Sci.
Gifu Univ., Fac. of Agric.
Hokkaido Univ., Fac. of Vet. Med.
St. Jude Children's Res. Hospital, Memphis

SOURCE: Nippon Bunshi Seibutsu Gakkai Nenkai Puroguramu, Koen Yoshishu, (1996) vol. 19th, pp. 90. Journal Code: L1278A

PUB. COUNTRY: Japan
LANGUAGE: Japanese
STATUS: New

L29 ANSWER 26 OF 29 MEDLINE on STN
ACCESSION NUMBER: 94292927 MEDLINE
DOCUMENT NUMBER: 94292927 PubMed ID: 7517433
TITLE: Sialoglycoproteins that bind **influenza** A virus and resist viral neuraminidase in different animal sera.

AUTHOR: Suzuki T; Tsukimoto M; Kobayashi M; Yamada A; **Kawaoka Y**; Webster R G; Suzuki Y

CORPORATE SOURCE: Department of Biochemistry, University of Shizuoka, School of Pharmaceutical Science, Japan.

CONTRACT NUMBER: AI-20591 (NIAID)
AI-29599 (NIAID)
CA-21765 (NCI)

SOURCE: JOURNAL OF GENERAL VIROLOGY, (1994 Jul) 75 (Pt 7) 1769-74.
Journal code: 0077340. ISSN: 0022-1317.

PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199408
ENTRY DATE: Entered STN: 19940815
Last Updated on STN: 19960129
Entered Medline: 19940804

AB Sialoglycoproteins that are resistant to degradation by viral neuraminidase can effectively neutralize **influenza** A viruses, because they bind irreversibly to the viruses. To detect such proteins in animal sera, we developed an immunochemical assay based on Western blotting techniques. We assessed the binding activity of sialoglycoproteins in sera from nine different animals toward the A/Aichi/2/68 (H3N2) and A/PR/8/34 (H1N1) strains of **influenza** virus, with or without viral and bacterial neuraminidase treatment. Using this assay, we found that animal sera contain a spectrum of sialoglycoproteins defined by differing abilities to bind **influenza** A viruses and to resist the viral neuraminidase. Structural analysis of these inhibitors would provide useful information for the development of anti-**influenza** virus compounds.

L29 ANSWER 27 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 19

ACCESSION NUMBER: 1994:696777 HCAPLUS
DOCUMENT NUMBER: 121:296777
TITLE: Receptor specificity in human, avian, and equine H2 and H3 **influenza** virus isolates
AUTHOR(S): Connor, Robert J.; **Kawaoka, Yoshihiro**; Webster, Robert G.; Paulson, James C.
CORPORATE SOURCE: Dep. Biological Chem., UCLA Sch. Med., Los Angeles, CA, 90024-1737, USA
SOURCE: Virology (1994), 205(1), 17-23
CODEN: VIRLAX; ISSN: 0042-6822
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The receptor specificity of 56 H2 and H3 **influenza** virus isolates from various animal spp. was determined to test the relevance of receptor specificity to the ecol. of **influenza** virus. The receptor specificity of both H2 and H3 isolates evaluated for **sialic** acid linkage specificity and inhibition of hemagglutination by horse serum correlated with the species of origin, as postulated earlier for H3 strains based on a limited survey of 5 human, 3 avian, and 1 equine strain. Elucidation of the amino acid sequences of several human H2 receptor variants and anal. of known sequences of H2 and H3 isolates revealed that receptor specificity varies in association with an amino acid change at residues 228 in addition to the change at residue 226 previously documented to affect receptor specificity of H3 but not H1 isolates. Residues 226 and 228 are leucine and serine in human isolates, which preferentially bind **sialic** acid α-2,6-galactose β-1,4-N-acetyl glucosamine (SAα2,6Gal), and glutamine and glycine in avian and equine isolates, which exhibit specificity for **sialic** acid α-2,3-galactose β-1,3-N-acetyl galactosamine (SAα2,3Gal). The results demonstrate that the correlation of receptor specificity and species of origin is maintained across both H2 and H3 **influenza** virus serotypes and provide compelling evidence that **influenza** virus hosts exert selective pressure to maintain the receptor specificity characteristics of strains isolated from that species.

L29 ANSWER 28 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 20
ACCESSION NUMBER: 1993:211216 HCAPLUS
DOCUMENT NUMBER: 118:211216
TITLE: α2-Macroglobulin is the major neutralizing inhibitor of **influenza** A virus in pig serum
AUTHOR(S): Ryan-Poirier, Kathleen A.; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: Dep. Virol., St. Jude Child. Res. Hosp., Memphis, TN, 38105, USA
SOURCE: Virology (1993), 193(2), 974-6
CODEN: VIRLAX; ISSN: 0042-6822
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Horse, pig, and rabbit sera contain distinct glycoprotein inhibitors of **influenza** A viruses that inhibit hemagglutinating activity and neutralize viral infectivity. Although α2-macroglobulin has been identified as the inhibitor in horse serum, the inhibitors in pig and rabbit sera have not been identified. As an initial step in elucidating the structural

differences among inhibitor mols., the authors sought to isolate the inhibitor in pig serum. The purified inhibitor decreased the hemagglutinating activity of **influenza** A virus, A/Los Angeles/2/87 (H3N2), and represented the majority of the virus-neutralizing activity in pig serum.,. The inhibitor corresponded in size to α2-macroglobulin and cross-reacted antigenically with human α2-macroglobulin. Characterization of the inhibitor's oligosaccharide moiety using linkage-specific lectins revealed the presence of **N-acetylneuraminic** acid-α2,6-galactose but not **N-acetylneuraminic** acid-α2,3-galactose. These data indicate that α2-macroglobulin is the major neutralizing inhibitor of **influenza** A virus in pig serum.

L29 ANSWER 29 OF 29 HCAPLUS COPYRIGHT 2003 ACS on STN DUPLICATE 21
ACCESSION NUMBER: 1991:60318 HCAPLUS
DOCUMENT NUMBER: 114:60318
TITLE: Distinct glycoprotein inhibitors of **influenza** A virus in different animal sera
AUTHOR(S): Ryan-Poirier, Kathleen A.; **Kawaoka, Yoshihiro**
CORPORATE SOURCE: Dep. Infect. Dis., St. Jude Child. Res. Hosp., Memphis, TN, 38105, USA
SOURCE: Journal of Virology (1991), 65(1), 389-95
CODEN: JOVIAM; ISSN: 0022-538X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Normal horse and guinea pig sera contain the glycoprotein inhibitor α2-macroglobulin, which inhibits the infectivity and hemagglutinating activity of **influenza** A viruses of the H2 and H3 subtypes. In the current study, the presence of inhibitors of **influenza** A virus in pig and rabbit sera was investigated. Variants of **influenza** virus type A/Los Angeles/2/87(H3N2) that were resistant to horse, pig, or rabbit serum were isolated. Anal. of the variant viruses with anti-hemagglutinin (HA) monoclonal antibodies revealed that antigenic changes occurred with the development of serum inhibitor resistance. Characterization of the inhibitors in pig and rabbit sera by using periodate and receptor-destroying enzyme demonstrated that carbohydrate is an important constituent of the active portion of both inhibitor mols. and that **sialic** acid is involved in the interaction of the inhibitors with **influenza** virus HA. Nucleotide sequence anal. of the HA mol. revealed that the serum-resistant variants each acquired a different set of amino acid alterations. The multiply resistant variants maintained the original amino acid changes and acquired addnl. changes. Sequence modifications in the HA involved the conserved amino acids within the receptor binding site (RBS) at position 137 and the second-shell RBS residues at positions 155 and 186. Amino acid changes also occurred within antigenic site A (position 145) and directly behind the receptor binding pocket (position 220). Amino acid alterations resulted in the acquisition of a potential glycosylation site at position 128 and the loss of potential glycosylation sites at positions 246 and 248. The localization of the amino acid changes in HA1 to the region of the RBS supports the concept of serum inhibitors as receptor analogs. The unique set of mutations acquired by the serum inhibitor-resistant variants strongly suggests

that horse, pig, and rabbit sera contain distinct glycoprotein inhibitors of **influenza** A virus.

FILE 'HOME' ENTERED AT 15:12:10 ON 18 DEC 2003

17/3,AB/40 (Item 27 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00429133
Method and formulation employing type II endoglycosidase
Verfahren und Formulierung unter Verwendung von Endoglycosidase vom Typ II
Methode et formulation employant l'endoglycosidase du type II
PATENT ASSIGNEE:
THE PROCTER & GAMBLE COMPANY, (200173), One Procter & Gamble Plaza, Cincinnati, Ohio 45202, (US), (applicant designated states: AT;BE;CH;DE;DK;ES;FR;GB;GR;IT;LI;LU;NL;SE)
GENENCOR INTERNATIONAL, INC., (1285780), 4 Cambridge Place, 1870 South Winston Road, Rochester, New York 14618, (US), (applicant designated states: AT;BE;CH;DE;DK;ES;FR;GB;GR;IT;LI;LU;NL;SE)
INVENTOR:
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Lad, Pushkaraj Jogannath, 814 N. Delaware St., Apt. 310, San Mateo, CA 94401, (US)
Goldstein, Irwin J., 3980 Loch Alpine Dr., Ann Arbor, MI 48103, (US)
Wolff, Ann Margaret, 4570 Boomer Road, Cincinnati, Ohio 45247, (US)
LEGAL REPRESENTATIVE:
Canonici, Jean-Jacques et al (57861), Procter & Gamble European Technical Center N.V. Temselaan 100, 1853 Strombeek-Bever, (BE)
PATENT (CC, No, Kind, Date): EP 425018 A2 910502 (Basic)
EP 425018 A3 911002
EP 425018 B1 961211
APPLICATION (CC, No, Date): EP 90202750 901016;
PRIORITY (CC, No, Date): US 428361 891027
DESIGNATED STATES: AT; BE; CH; DE; DK; ES; FR; GB; GR; IT; LI; LU; NL; SE
INTERNATIONAL PATENT CLASS: C11D-003/386; C11D-003/00; A61K-007/48;

ABSTRACT EP 425018 A2
Methods and formulations for removing glycoside-containing substances from surfaces by treatment with Type II endoglycosidase alone or in combination with other enzymes and/or detergents.
ABSTRACT WORD COUNT: 28

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	EPABF1	950
CLAIMS B	(English)	EPAB96	982
CLAIMS B	(German)	EPAB96	972
CLAIMS B	(French)	EPAB96	1109
SPEC A	(English)	EPABF1	18610
SPEC B	(English)	EPAB96	18501
Total word count - document A			19562
Total word count - document B			21564
Total word count - documents A + B			41126

17/3,AB/41 (Item 28 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00429132

Method employing type II endoglycosidase
Verfahren unter Verwendung von Endoglycosidase vom Typ II
Methode employant l'endoglycosidase du type II
PATENT ASSIGNEE:
THE PROCTER & GAMBLE COMPANY, (200173), One Procter & Gamble Plaza, Cincinnati, Ohio 45202, (US), (applicant designated states: BE;DE;DK;FR;GB;IT;NL)
GENENCOR INTERNATIONAL, INC., (1285784), 4 Cambridge Place, 1870 South Winton Road, Rochester, New York 14618, (US), (applicant designated states: BE;DE;DK;FR;GB;IT;NL)
INVENTOR:
Carpenter, Richard Shepard, 10655 Gloria Ave., Cincinnati, Ohio 45231, (US)
Wolff, Ann Margaret, 4570 Boomer Road, Cincinnati, Ohio 45247, (US)
Lad, Pushkaraj Jogannath, 814 N. Delaware St., Apt. 310, San Mateo, CA 94401, (US)
LEGAL REPRESENTATIVE:
Canonici, Jean-Jacques et al (57861), Procter & Gamble European Technical Center N.V. Temselaan 100, B-1853 Strombeek-Bever, (BE)
PATENT (CC, No, Kind, Date): EP 425017 A2 910502 (Basic)
EP 425017 A3 911002
EP 425017 B1 951220
APPLICATION (CC, No, Date): EP 90202749 901016;
PRIORITY (CC, No, Date): US 428248 891027
DESIGNATED STATES: BE; DE; DK; FR; GB; IT; NL
INTERNATIONAL PATENT CLASS: C11D-003/386; C11D-003/00; A61K-007/48;

ABSTRACT EP 425017 A2
Methods for removing microorganisms, such as bacteria, from surfaces by treatment with Type II endoglycosidase alone or in combination with other enzymes and/or detergents.
ABSTRACT WORD COUNT: 28

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	EPABF1	271
CLAIMS B	(English)	EPAB95	262
CLAIMS B	(German)	EPAB95	270
CLAIMS B	(French)	EPAB95	291
SPEC A	(English)	EPABF1	18293
SPEC B	(English)	EPAB95	18067
Total word count - document A			18566
Total word count - document B			18890
Total word count - documents A + B			37456

17/3,AB/42 (Item 29 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00429131
Antimicrobial method and formulation employing type II endoglycosidase and antimicrobial agent
Antimikrobielles Verfahren und Formulierung unter Verwendung von Endoglycosidase vom Typ II und antimikrobielles Mittel
Methode antimicrobienne et formulation employant l'endoglycosidase du type II et agent antimicrobien

PATENT ASSIGNEE:
THE PROCTER & GAMBLE COMPANY, (200173), One Procter & Gamble Plaza, Cincinnati, Ohio 45202, (US), (applicant designated states: BE;DE;DK;FR;GB;IT;NL)
GENENCOR INTERNATIONAL, INC., (1285784), 4 Cambridge Place, 1870 South Winton Road, Rochester, New York 14618, (US), (applicant designated states: BE;DE;DK;FR;GB;IT;NL)
INVENTOR:
Carpenter, Richard Shepard, 10655 Gloria Ave., Cincinnati, Ohio 45231, (US)
Wolff, Ann Margaret, 4570 Boomer Road, Cincinnati, Ohio 45247, (US)
Lad, Pushkaraj Jogannath, 203 Falguni Ashoknagar, Kandivali (E) Bombay 400101, (IN)
LEGAL REPRESENTATIVE:
Canonici, Jean-Jacques et al (57861), Procter & Gamble European Technical Center N.V. Temselaan 100, B-1853 Strombeek-Bever, (BE)
PATENT (CC, No, Kind, Date): EP 425016 A2 910502 (Basic)
EP 425016 A3 911002
EP 425016 B1 951220
APPLICATION (CC, No, Date): EP 90202748 901016;
PRIORITY (CC, No, Date): US 428362 891027
DESIGNATED STATES: BE; DE; DK; FR; GB; IT; NL
INTERNATIONAL PATENT CLASS: C11D-003/386; C11D-003/00; A61K-007/48;

ABSTRACT EP 425016 A2
Antimicrobial methods and antimicrobial compositions utilizing Type II endoglycosidase alone or in combination with an antimicrobial agent.
ABSTRACT WORD COUNT: 21

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS A	(English)	EPABF1	922
CLAIMS B	(English)	EPAB95	895
CLAIMS B	(German)	EPAB95	869
CLAIMS B	(French)	EPAB95	1086
SPEC A	(English)	EPABF1	18337
SPEC B	(English)	EPAB95	18116
Total word count - document A			19261
Total word count - document B			20966
Total word count - documents A + B			40227

17/3,AB/43 (Item 30 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00413243
Preventive and curative medicament against infection with **influenza virus**, containing tea or tea polyphenols.
Thee oder Thee-Polyphenole enthaltendes Vorbeugungs- und Behandlungsmittel gegen Influenzavireninfektion.
Medicament preventif et curatif contre l'infection du virus de la grippe, renfermant du the ou des polyphenols du the.
PATENT ASSIGNEE:
MITSUI NORIN CO., LTD., (947690), 1-20, 3-chome, Nihonbashimuromachi Chuo-ku, Tokyo, (JP), (applicant designated states: AT;BE;CH;DE;ES;FR;GB;IT;LI;LU;NL;SE)

Shimamura, Tadakatsu, (1224190), 4-4, Nishihara 1-chome, Shibuya-ku, Tokyo, (JP), (applicant designated states: AT;BE;CH;DE;ES;FR;GB;IT;LI;LU;NL;SE)
INVENTOR:
Shimamura, Tadakatsu, 4-4, Nishihara 1-chome, Shibuya-ku, Tokyo, (JP)
Hara, Yukihiko, 2-7, Minamisurugadai 2-chome, Fujieda-shi, Shizuoka-ken, (JP)
LEGAL REPRESENTATIVE:
Turk, Gille, Hrabal, Leifert (100971), Brucknerstrasse 20, D-40593 Dusseldorf, (DE)
PATENT (CC, No, Kind, Date): EP 417385 A2 910320 (Basic)
EP 417385 A3 910424
EP 417385 B1 940720
APPLICATION (CC, No, Date): EP 90107386 900419;
PRIORITY (CC, No, Date): JP 89236950 890914
DESIGNATED STATES: AT; BE; CH; DE; ES; FR; GB; IT; LI; LU; NL; SE
INTERNATIONAL PATENT CLASS: A61K-035/78; A61K-031/35;

ABSTRACT EP 417385 A2
The effective ingredient in the inventive medicament against infection with **influenza virus** is tea, e.g., black tea, or a tea polyphenol as a constituent of tea including epigallocatechin gallate, epicatechin gallate, epigallocatechin, epicatechin, (+)catechin and the isomer thereof, free theaflavin, theaflavin monogallates A and B and theaflavin digallate.
ABSTRACT WORD COUNT: 52

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	EPBBF1	77
CLAIMS B	(German)	EPBBF1	61
CLAIMS B	(French)	EPBBF1	102
SPEC B	(English)	EPBBF1	2268
Total word count - document A			0
Total word count - document B			2508
Total word count - documents A + B			2508

17/3,AB/44 (Item 31 from file: 348)
DIALOG(R)File 348:EUROPEAN PATENTS

00351509
Glycosylated polypeptides
Glykosylierte Polypeptide
Polypeptides glycosyles
PATENT ASSIGNEE:
Kyowa Hakko Kogyo Co., Ltd., (229066), 6-1, Ohtemachi 1-chome, Chiyoda-ku, Tokyo 100, (JP), (applicant designated states: AT;BE;CH;DE;ES;FR;GB;GR;IT;LI;LU;NL;SE)
INVENTOR:
Sasaki, Katsutoshi, 3-6-6, Asahi-machi, Machida-shi Tokyo, (JP)
Nishi, Tatsunari, 3-9-11, Naka-machi, Machida-shi Tokyo, (JP)
Yasumura, Shigeyoshi, 3-6-6, Asahi-machi, Machida-shi Tokyo, (JP)
Sato, Moriyuki, 2730-15, Naruse, Machida-shi Tokyo, (JP)
Itoh, Seiga, 6-9-48, Aihara, Sagamihara-shi Kanagawa, (JP)
LEGAL REPRESENTATIVE:

Kinzebach, Werner, Dr. et al (6468), Patentanwalte Reitstotter, Kinzebach und Partner Postfach 86 06 49, 81633 Munchen, (DE)
PATENT (CC, No, Kind, Date): EP 370205 A2 900530 (Basic)
EP 370205 A3 900613
EP 370205 B1 980722
APPLICATION (CC, No, Date): EP 89117981 890928;
PRIORITY (CC, No, Date): JP 88245705 880929
DESIGNATED STATES: AT; BE; CH; DE; ES; FR; GB; GR; IT; LI; LU; NL; SE
INTERNATIONAL PATENT CLASS: C07K-014/535; C12N-015/27; C12N-001/21; C12N-005/10; A61K-038/19;

ABSTRACT EP 370205 A2
A polypeptide or glycosylated polypeptide with at least one new carbohydrate chain produced by means of recombinant DNA technique, which has protease resistance and thermal stability and is expected to have longer lifetime in blood than those of a naturally-occurring form.
ABSTRACT WORD COUNT: 45

LANGUAGE (Publication,Procedural,Application): English; English; English
FULLTEXT AVAILABILITY:

Available Text	Language	Update	Word Count
CLAIMS B	(English)	9830	2052
CLAIMS B	(German)	9830	1823
CLAIMS B	(French)	9830	2191
SPEC B	(English)	9830	27507
Total word count - document A			0
Total word count - document B			33573
Total word count - documents A + B			33573

17/3,AB/45 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0301645 DBR Accession No.: 2003-03430 PATENT
New **mutant** cell for propagating **influenza virus** with **decreased** sialidase activity useful as vaccine, comprises **decreased** levels of **sialic** acid containing host cell receptors for **influenza virus** - packaging cell culture for **influenza** A **virus** and **influenza** B **virus** infection recombinant vaccine, nucleic acid vaccine and gene therapy
AUTHOR: KAWAOKA Y
PATENT ASSIGNEE: WISCONSIN ALUMNI RES FOUND; KAWAOKA Y 2002
PATENT NUMBER: WO 200268632 PATENT DATE: 20020906 WPI ACCESSION NO.: 2002-706991 (200276)
PRIORITY APPLIC. NO.: US 271044 APPLIC. DATE: 20010223
NATIONAL APPLIC. NO.: WO 2002US5455 APPLIC. DATE: 20020222
LANGUAGE: English
ABSTRACT: DERWENT ABSTRACT: NOVELTY - An isolated **mutant** cell (I) comprising **decreased** levels of **sialic** acid containing host cell receptors for **influenza virus** relative to a corresponding wild-type cell which supports efficient **influenza virus** replication, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) isolating a cell that has **decreased** levels of receptors for **influenza virus** , comprising: (a) contacting a population of cells permissive for **influenza virus** replication and sensitive to lectin or agglutinin growth inhibition with an amount of lectin or agglutinin to

yield cells that are resistant to growth inhibition by the lectin or agglutinin that specifically binds **sialic** acid; and (b) isolating a lectin- or agglutinin-resistant cell having **decreased** levels of receptors for **influenza virus** ; (2) a lectin- or agglutinin-resistant cell isolated by method (1); (3) propagating **influenza viruses** having **reduced** sialidase activity by contacting (I) and the lectin- or agglutinin-resistant cell with an amount of an **influenza virus** having **reduced** sialidase activity to yield progeny virus; (4) a progeny virus obtained by method (3); (5) using a host cell having **decreased** levels of **sialic** acid containing host cell receptors for **influenza virus** , comprising: (a) contacting (I) and the lectin- or agglutinin-resistant cell with an amount of an **influenza virus** having wild-type levels of sialidase activity to yield progeny virus; and (b) serially propagating the progeny virus with (I) and the lectin- or agglutinin-resistant cell to yield adapted viruses that efficiently replicate in the **mutant** cell and the lectin- or agglutinin-resistant cell; and (6) isolated adapted virus obtained by method (5), which does not have a **mutation** in the hemagglutinin (HA) gene relative to the virus having substantially wild-type levels of sialidase activity. WIDER DISCLOSURE - Eliciting an immune response to an **influenza virus** , which may be prophylactic or therapeutic for an **influenza virus** infection. BIOTECHNOLOGY - Preferred **Cell**: The mutant **cell** is a mammalian **cell** , particularly **swine, bovine, simian** or **canine cell**. Alternatively, the mutant **cell** is a **mink** lung **cell**, or an **avian cell**. The wild-type **cell** is **MDCK cell**. The mutant **cell** has **decreased** levels of **N-acetylneuraminic** acid and/or **N-glycolylneuraminic** acid, particularly at least 10-fold lower levels of **N-acetylneuraminic** acid and at least 2-fold lower levels of **N-glycolylneuraminic** acid relative to the corresponding wild-type cell. The lectin-resistant cell is resistant to growth inhibition by Maakia amurensis or Sambucus nigra lectin. Preferred Method: In isolating a cell that has **decreased** levels of receptors for **influenza virus**, the lectin is Maakia amurensis, Sambucus nigra or Tritrichomonas mobilensis lectin. The agglutinin is Limax flavus agglutinin. The lectin specifically binds **sialic** acid linked to galactose by alpha(2-3) or alpha(2-6) linkages, or to N-acetylgalactosamine by alpha(2-6) linkages. The method of using a host cell having **decreased** levels of **sialic** acid containing host cell receptors for **influenza virus** , further comprises isolating the adapted virus. In method (3) or (5), the **influenza virus** is particularly type A or B **influenza virus** . ACTIVITY - Virucide; Immunomodulator. No biological data is given. MECHANISM OF ACTION - Vaccine; Gene therapy. USE - The **mutant** cell is useful in propagating **influenza virus** having **reduced** or **decreased** sialidase activity. The obtained virus may be employed in vaccines, in preparing monoclonal or polyclonal antibodies specific for those viruses, in preparing recombinant or reassortant viruses, or for gene delivery including the delivery of immunogenic non-**influenza virus** proteins or peptide for vaccines or therapeutic proteins. ADMINISTRATION - The dosage of attenuated virus may range from 103-107 plaque-forming units (PFU)/kg. The inactivated vaccine can be given at a dose of 0.1-200 microg HA protein. Administration is by subcutaneous, intravenous, intradermal, intramuscular, intraperitoneal, intranasal, oral or transdermal routes. EXAMPLE - No relevant examples given. (33 pages)

Set	Items	Description
S19	34	S12 AND REDUCTION
S20	9	S19 NOT S13
S21	1	RD (unique items)

>>>No matching display code(s) found in file(s): 65, 113

21/3,AB/1 (Item 1 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

12967368 References: 53
TITLE: Apoptosis by **influenza viruses** correlates with efficiency of viral mRNA synthesis
AUTHOR(S): Stray SJ; Air GM (REPRINT)
AUTHOR(S) E-MAIL: gillian-air@ouhsc.edu
CORPORATE SOURCE: Univ Oklahoma, Dept Biochem & Mol Biol, POB 26901/Oklahoma City//OK/73190 (REPRINT); Univ Oklahoma, Dept Biochem & Mol Biol, /Oklahoma City//OK/73190; Univ Alabama, Microbiol Grad Program, /Birmingham//AL/
PUBLICATION TYPE: JOURNAL
PUBLICATION: VIRUS RESEARCH, 2001, V77, N1 (SEP), P3-17
GENUINE ARTICLE#: 462LH
PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
ISSN: 0168-1702
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: A **mutant influenza virus**, A/NWS-Mvi, grows well in the presence of exogenous sialidase activity sufficient to remove all cell surface **sialic** acids. Related wild-type viruses grow very poorly under these conditions, although **mutant** and wild-type viruses bind to desialylated cells with similar efficiency and show similar **reduction** of binding to sialidase-treated cells compared to native cells. Here we examine entry, transcription, translation, and RNA replication and find that, although the viruses appear to utilize the same entry pathway, the **mutant** NWS-Mvi transcribes and replicates RNA to higher levels than the wild-type strains. The kinetics of replication in multi-cycle infection show that this enhancement of RNA synthesis facilitates growth where entry is restricted. The hemagglutinin (HA) protein of NWS-Mvi lyses red blood cells 0.1 pH unit higher than wild-type viruses. This higher fusion pH may allow more efficient release of nucleocapsids from endosomes and contribute to the enhanced RNA synthesis. The efficient RNA synthesis assists virus survival at low inocula or under stringent growth conditions, such as the presence of antiviral agents. NWS-Mvi induces apoptosis in infected cells more readily than wild-type viruses, apparently as a consequence of enhanced production of viral mRNA. Since growth of NWS-Mvi is more efficient, apoptosis may play a positive role in viral replication by removing cells that have already been infected from those capable of making more virus. (C) 2001 Elsevier Science B.V. All rights reserved.

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*File 113: This file is closed (no updates)

Set Items Description
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Set Items Description — Author
S1 462 AU=(KAWAOKA, Y? OR KAWAOKA Y?)
S2 15204 SIALIC OR N(W)(ACETYLNEURAMINIC OR GLYCOLYLNEURAMINIC OR (-ACETYL OR AC OR GLYCOLYL)(W)(NEU OR NEURAMINIC)) OR NEUNAC OR NEU(W)(NAC OR GC) OR NEUGC
S3 41 S1 AND S2
S4 38 S3 AND INFLUENZ?
S5 21 RD (unique items)
S6 10 S5 AND CELL? ?
>>>No matching display code(s) found in file(s): 65, 113

6/3,AB/1 (Item 1 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)
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12959842 References: 52
TITLE: **Sialic** acid species as a determinant of the host range of **influenza** A viruses
AUTHOR(S): Suzuki Y; Ito T; Suzuki T; Holland RE; Chambers TM; Kiso M; Ishida H; **Kawaoka Y (REPRINT)**
AUTHOR(S) E-MAIL: kawaokay@svm.vetmed.wisc.edu
CORPORATE SOURCE: Univ Wisconsin, Dept Pathobiol Sci, 2015 Linden Dr W/Madison//WI/53706 (REPRINT); Univ Wisconsin, Dept Pathobiol Sci, /Madison//WI/53706; Univ Shizouka, Dept Biochem, /Shizuoka 4228526//Japan/; Tottori Univ, Dept Vet Publ Hlth, /Tottori 6808553//Japan/; Gifu Univ, Dept Appl Bioorgan Chem, /Gifu 5011193//Japan/; Univ Tokyo, Minato Ku, /Tokyo 1088639//Japan/; Univ Kentucky, Dept Vet Sci, /Lexington//KY/40546
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF VIROLOGY, 2000, V74, N24 (DEC), P11825-11831
GENUINE ARTICLE#: 461LN
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA

Searcher : Shears 308-4994

ISSN: 0022-538X
LANGUAGE: English DOCUMENT TYPE: ARTICLE
ABSTRACT: The distribution of **sialic** acid (SA) species varies among animal species, but the biological role of this variation is largely unknown. **Influenza** viruses differ in their ability to recognize SA-galactose (Gal) linkages, depending on the animal hosts from which they are isolated. For example, human viruses preferentially recognize SA linked to Gal by the alpha2,6(SA alpha2,6Gal) linkage, while equine viruses favor SA alpha2,3Gal. However, whether a difference in relative abundance of specific SA species (**N-acetylneuraminic** acid [NeuAc] and **N-glycolylneuraminic** acid [**NeuGc**]) among different animals affects the replicative potential of **influenza** viruses is uncertain. We therefore examined the requirement for the hemagglutinin (HA) for support of viral replication in horses, using viruses whose HAs differ in receptor specificity. A virus with an HA recognizing NeuAc alpha2,6Gal but not NeuAc alpha2,3Gal or NenGc alpha2,3Gal failed to replicate in horses, while one with an HA recognizing the **NeuGc** alpha2,3Gal moiety replicated in horses. Furthermore, biochemical and immunohistochemical analyses and a lectin-binding assay demonstrated the abundance of the NeuGca2,3Gal moiety in epithelial **cells** of horse trachea, indicating that recognition of this moiety is critical for viral replication in horses. Thus, these results provide evidence of a biological effect of different SA species in different animals.

6/3,AB/2 (Item 2 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

12553933 References: 29
TITLE: Adaptation of **influenza** A viruses to **cells** expressing low levels of **sialic** acid leads to loss of neuraminidase activity
AUTHOR(S): Hughes MT; McGregor M; Suzuki T; Suzuki Y; **Kawaoka Y (REPRINT)**
AUTHOR(S) E-MAIL: kawaokay@svm.vetmed.wisc.edu
CORPORATE SOURCE: Univ Wisconsin, Dept Pathobiol Sci, 2015 Linden Dr W/Madison//WI/53706 (REPRINT); Univ Wisconsin, Dept Pathobiol Sci, /Madison//WI/53706; Univ Tennessee, Dept Pathol, /Memphis//TN/38163; Univ Shizouka, Dept Biochem, /Shizuoka 4228526//Japan/; Univ Tokyo, Inst Med Sci, /Tokyo 1088639//Japan/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF VIROLOGY, 2001, V75, N8 (APR), P3766-3770
GENUINE ARTICLE#: 414QN
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
ISSN: 0022-538X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: **Influenza** A viruses possess two virion surface proteins, hemagglutinin (HA) and neuraminidase (NA). The HA binds to sialyloligosaccharide viral receptors, while the NA removes **sialic** acids from the host **cell** and viral sialyloligosaccarides. Alterations of the HA occur during adaptation of **influenza** viruses to new host species, as in the 1957 and 1968 **influenza** pandemics. To gain a better understanding of the contributions of the HA and possibly the NA to this process, we generated **cell** lines expressing reduced levels of the **influenza** virus receptor determinant, **sialic** acid, by selecting Madin-Darby canine kidney **cells** resistant to a lectin

specific for **sialic** acid linked to galactose by alpha (2-3) or alpha (2-6) linkages, One of these **cell** lines had less than 1/10 as much **N-acetylneuraminic** acid as its parent **cell** line. When serially passaged in this **cell** line, human H3N2 viruses lost sialidase activity due to a large internal deletion in the NA gene, without alteration of the HA gene. These findings indicate that NA mutations can contribute to the adaptation of **influenza** A virus to new host environments and hence may play a role in the transmission of virus across species.

6/3,AB/3 (Item 3 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

11991205 References: 37
TITLE: Recognition of **N-glycolylneuraminic** acid linked to galactose by the alpha 2,3 linkage is associated with intestinal replication of **influenza** A virus in ducks
AUTHOR(S): Ito T; Suzuki Y; Suzuki T; Takda A; Horimoto T; Wells K; Kida H; Otsuki K; Kiso M; Ishida H; **Kawaoka Y (REPRINT)**
AUTHOR(S) E-MAIL: kawaokay@svm.vetmed.wisc.edu
CORPORATE SOURCE: Univ Wisconsin, Dept Pathobiol Sci, 2015 Linden Dr W/Madison//WI/53706 (REPRINT); Univ Wisconsin, Dept Pathobiol Sci, /Madison//WI/53706; Tottori Univ, Dept Vet Publ Hlth, /Tottori 6808553//Japan/; Univ Shizuoka, Dept Biochem, /Shizuoka 4228002//Japan/; Hokkaido Univ, Microbiol Lab, /Sapporo/Hokkaido 0600818/Japan/; Univ Osaka Prefecture, Dept Vet Microbiol, /Sakai/Osaka 5996231/Japan/; Gifu Univ, Dept Appl Bioorgan Chem, /Gifu 5011193//Japan/; Univ Tokyo, Minato Ku, /Tokyo 1088639//Japan/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF VIROLOGY, 2000, V74, N19 (OCT), P9300-9305
GENUINE ARTICLE#: 352XH
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
ISSN: 0022-538X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: The hemagglutinin (IU) of H3 human **influenza** viruses does not support viral replication in duck intestine despite its avian origin. A Leu-to-Gin mutation at position 226 and a Ser-to-Gly mutation at position 228 in the HA of human A/Udorn/307/72 (H3N2) permit a reassortant virus [human Udorn HA, with all other genes from A/mallard/New York/6750/78 (H2N2)] to replicate in ducks. To understand the molecular basis of this change in host range restriction, we investigated the receptor specificity of duck **influenza** viruses as well as of human-duck virus reassortants. The results indicate that the recognition of a glycoconjugate moiety possessing N-glycolneuramic acid (**NeuGc**) linked to galactose by the alpha 2,3 linkage (**NeuGc** alpha 2,3Gal) is associated with viral replication in duck intestine. Immunofluorescence assays with **NeuGc** alpha 2,3Gal-specific antiserum detected this moiety primarily on the crypt epithelial **cells** of duck colon. Such recognition, together with biochemical evidence of **NeuGc** in crypt **cells**, correlated exactly with the ability of the virus to replicate in duck colon. These results suggest that recognition of the **NeuGc** alpha 2,3-Gal moiety plays an important role in the enterotropism of avian **influenza** viruses.

6/3,AB/4 (Item 4 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

11610113 References: 33
TITLE: **Influenza** A viruses lacking sialidase activity can undergo multiple cycles of replication in **cell** culture, eggs, or mice
AUTHOR(S): Hughes MT; Matrosovich M; Rodgers ME; McGregor M; **Kawaoka Y (REPRINT)**
AUTHOR(S) E-MAIL: kawaokay@svm.vetmed.wisc.edu
CORPORATE SOURCE: Univ Wisconsin, Dept Pathobiol Sci, 2015 Linden Dr W/Madison//WI/53706 (REPRINT); Univ Wisconsin, Dept Pathobiol Sci, /Madison//WI/53706; Univ Tennessee, Dept Pathol, /Memphis//TN/38163; St Jude Childrens Res Hosp, Dept Virol & Mol Biol, /Memphis//TN/38105; MP Chumakov Inst Poliomyelitis & Viral Encephalit, /Moscow 142782//Russia/
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF VIROLOGY, 2000, V74, N11 (JUN), P5206-5212
GENUINE ARTICLE#: 312MX
PUBLISHER: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
ISSN: 0022-538X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: **Influenza** A viruses possess both hemagglutinin (HA), which is responsible for binding to the terminal **sialic** acid of sialyloligosaccharides on the **cell** surface, and neuraminidase (NA), which contains sialidase activity that removes **sialic** acid from sialyloligosaccharides. Interplay between HA receptor-binding and NA receptor-destroying sialidase activity appears to be important for replication of the virus. Previous studies by others have shown that **influenza** A viruses lacking sialidase activity can undergo multiple cycles of replication if sialidase activity is provided exogenously. To investigate the sialidase requirement of **influenza** viruses further, we generated a series of sialidase-deficient mutants. Although their growth was less efficient than that of the parental NA-dependent virus, these viruses underwent multiple cycles of replication in **cell** culture, eggs, and mice. To understand the molecular basis of this viral growth adaptation in the absence of sialidase activity, we investigated changes in the HA receptor-binding affinity of the sialidase-deficient mutants, The results show that mutations around the HA receptor-binding pocket reduce the virus's affinity for cellular receptors, compensating for the loss of sialidase, Thus, sialidase activity is not absolutely required in the **influenza** A virus life cycle but appears to be necessary for efficient virus replication.

6/3,AB/5 (Item 5 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

11230108 References: 31
TITLE: Substitution of amino acid residue in **influenza** A virus hemagglutinin affects recognition of sialyl-oligosaccharides containing **N-glycolylneuraminic** acid
AUTHOR(S): Masuda H; Suzuki T; Sugiyama Y; Horiike G; Murakami K; Miyamoto D; Hidari KIPJ; Ito T; Kida H; Kiso M; Fukunaga K; Ohuchi M; Toyoda T; Ishihama A; **Kawaoka Y**; Suzuki Y (REPRINT)

AUTHOR(S) E-MAIL: suzukiy@ys7.u-shizuoka-ken.ac.jp
CORPORATE SOURCE: Univ Shizouka, Dept Biochem, /Shizouka 4228526//Japan/ (REPRINT); Univ Shizouka, Dept Biochem, /Shizouka 4228526//Japan/; Tottori Univ, Dept Vet Publ Hlth, /Tottori 6808553//Japan/; Hokkaido Univ, Dept Dis Control, /Sapporo/Hokkaido 0600818/Japan/; Gifu Univ, Dept Appl Bioorgan Chem, /Gifu 5011193//Japan/; Kawasaki Med Sch, Dept Microbiol, /Kurashiki/Okayama 7010192/Japan/; Kurume Univ, Dept Virol, /Kurume/Fukuoka 8300011/Japan/; Natl Inst Genet, Dept Mol Genet, /Mishima/Shizuoka 4118540/Japan/; Univ Wisconsin, Dept Pathobiol Sci, /Madison//WI/53706
PUBLICATION TYPE: JOURNAL
PUBLICATION: FEBS LETTERS, 1999, V464, N1-2 (DEC 24), P71-74
GENUINE ARTICLE#: 272MQ
PUBLISHER: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
ISSN: 0014-5793
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: **Sialic** acids are essential components of **cell** surface receptors used by **influenza** viruses. To determine the molecular mechanisms of viral recognition of two major species of **sialic** acids, **N-acetylneuraminic** acid (Neu5Ac) and **N-glycolylneuraminic** acid (Neu5Gc), we tested the binding reactivity of nine human H3 **influenza** A viruses to sialylglycolipids containing type II sugar chain and different molecular species of terminal **sialic** acids, All human H3 viruses tested except A/Memphis/1/71 bound both Neu5Ac and Neu5Gc, Nucleotide sequence analysis suggests that amino acids at 143, 155, and 158 are linked to the viral recognition of Neu5Gc.

6/3,AB/6 (Item 6 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

09024230 References: 39
TITLE: Mutations affecting the sensitivity of the **influenza** virus neuraminidase to 4-guanidino-2,4-dideoxy-2,3-dehydro-N-**acetylneuraminic** acid
AUTHOR(S): Goto H; Bethell RC; **Kawaoka Y (REPRINT)**
CORPORATE SOURCE: UNIV WISCONSIN,SCH VET MED, DEPT PATHOBIOL SCI, 2015 LINDEN DR W/MADISON//WI/53706 (REPRINT); ST JUDE CHILDRENS HOSP,DEPT VIROL & MOL BIOL/MEMPHIS//TN/38101; GLAXO GRP RES LTD,/GREENFORD UB6 0HE/MIDDX/ENGLAND/; UNIV TENNESSEE,CTR HLTH SCI, DEPT PATHOL/MEMPHIS//TN/38163
PUBLICATION TYPE: JOURNAL
PUBLICATION: VIROLOGY, 1997, V238, N2 (NOV 24), P265-272
GENUINE ARTICLE#: YK656
PUBLISHER: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
ISSN: 0042-6822
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: 4-Guanidino-2,4-dideoxy-2,3-dehydro-N-acethylneuraminic acid (4-guanidino-Neu5Ac2en) specifically inhibits the **influenza** virus neuraminidase (NA) through interaction of the guanidino group with conserved Glu 119 and Glu 227 residues in the substrate binding pocket of the enzyme. To understand the mechanism by which **influenza** viruses become resistant to 4-guanidino-Neu5Ac2en, we investigated mutations at

amino acid residues 119 and 227 in the **influenza** virus NA for their effects on this compound and on NA activity. The NA gene was cloned from the NWS-G70c virus, and mutations were introduced at the codon for amino acid residue 119 or 227. All of the 13 mutants containing a change at residue 110 were transported to the **cell** surface, although their expression levels ranged from 68.2 to 91.3% of wild type. Mutant NAs that retained at least 20% of the wild-type enzymatic activity were tested for their sensitivity to 4-guanidino-Neu5Ac2en and found to be sevenfold less sensitive to this compound than was the wild-type NA By contrast, only 6 of 13 mutants defined by modifications at residue 227 were transported to the **cell** surface, and those NAs lacked substantial enzymatic activity (9% of wild type, at most). These results suggest that only a limited number of resistant viruses arise through mutations at Glu 119 and Glu 227 under selective pressure from 4-guanidino-Neu5Ac2en and that the development of compounds which interact with 227 Glu more strongly than does 4-guanidino-NeusAc2en may reduce the likelihood of drug-resistant viruses still further. (C) 1997 Academic Press.

6/3,AB/7 (Item 7 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

08275661 References: 35
TITLE: Differences in **sialic** acid-galactose linkages in the chicken egg amnion and allantois influence human **influenza** virus receptor specificity and variant selection
AUTHOR(S): Ito T; Suzuki Y; Takada A; Kawamoto A; Otsuki K; Masuda H; Yamada M; Suzuki T; Kida H; **Kawaoka Y (REPRINT)**
CORPORATE SOURCE: ST JUDE CHILDRENS HOSP,DEPT VIROL & MOL BIOL, 332 N LAUDERDALE, POB 318/MEMPHIS//TN/38101 (REPRINT); ST JUDE CHILDRENS HOSP,DEPT VIROL & MOL BIOL/MEMPHIS//TN/38101; HOKKAIDO UNIV,GRAD SCH VET MED, DEPT DIS CONTROL, MICROBIOL LAB/SAPPORO/HOKKAIDO 060/JAPAN/; TOTTORI UNIV,FAC AGR, DEPT VET PUBL HLTH/TOTTORI 680//JAPAN/; TOTTORI PREFECTURE INST HLTH,/TOTTORI 680//JAPAN/; SHIZUOKA UNIV,SCH PHARMACEUT SCI, DEPT BIOCHEM/SHIZUOKA 422//JAPAN/; UNIV TENNESSEE,DEPT PATHOL/MEMPHIS//TN/38163
PUBLICATION TYPE: JOURNAL
PUBLICATION: JOURNAL OF VIROLOGY, 1997, V71, N4 (APR), P3357-3362
GENUINE ARTICLE#: WM911
PUBLISHER: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171
ISSN: 0022-538X
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Human **influenza** viruses are more efficiently isolated by inoculating patient samples into the amniotic rather than the allantoic cavity of embryonated chicken eggs, This type of cultivation selects virus variants with mutations around the hemagglutinin (HA) receptor binding site. To understand the molecular basis of these phenomena, we investigated the abundances of **sialic** acid (SA) linked to galactose (Gal) by the alpha-2,3 linkage (SA alpha 2,3Gal) and SA alpha 2,6Gal in egg amniotic and allantoic **cells** and in Madin-Darby canine kidney (MDCK) **cells**, Using SA-Gal linkage-specific lectins (Maackia amurensis agglutinin specific for SA alpha 2,6Gal and Sambucus nigra agglutinin specific for SA alpha 2,3Gal), we found SA alpha 2,3Gal in both allantoic and amniotic **cells** and SA alpha 2,6Gal in only the amniotic **cells**, MDCK; **cells** contained both linkages, To investigate how this difference in

abundances of SA alpha 2,3Gal and SA alpha 2,6Gal in allantoic and amniotic **cells** affects the appearance of host **cell** variants in eggs, we determined the receptor specificities and HA amino acid sequences of two different patient viruses which were isolated and passaged in the amnion or in the allantois and which were compared with MDCK **cell** grown viruses, We found that the viruses maintained high SA alpha 2,6Gal specificities when grown in MDCK **cells** or following up to two amniotic passages; however, further passages in either the amnion or allantois resulted in the acquisition of, or a complete shift to, SA alpha 2,3Gal specificity, depending on the virus strain. This change in receptor specificity was accompanied by the appearance of variants in the population with Leu-to Gln mutations at position 226 in their HA, These findings suggest that lack of SA alpha 2,6Gal linkages in the allantois of chicken eggs is a selective pressure for the appearance of host **cell** variants with altered receptor specificities and amino acid changes at position 226.

6/3,AB/8 (Item 8 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

08117805 References: 36
TITLE: Receptor specificity of **influenza** A viruses correlates with the agglutination of erythrocytes from different animal species
AUTHOR(S): Ito T (REPRINT); Suzuki Y; Mitnaul L; Vines A; Kida H; **Kawaoka Y**
CORPORATE SOURCE: TOTTORI UNIV,FAC AGR, DEPT VET PUBL HLTH/TOTTORI 680//JAPAN/ (REPRINT); HOKKAIDO UNIV,GRAD SCH VET MED, DEPT DIS CONTROL, MICROBIOL LAB/SAPPORO/HOKKAIDO 060/JAPAN/; UNIV SHIZUOKA,SCH PHARMACEUT SCI, DEPT BIOCHEM/SHIZUOKA 422//JAPAN/; ST JUDE CHILDRENS HOSP,DEPT VIROL & MOL BIOL/MEMPHIS//TN/38101; UNIV TENNESSEE,DEPT PATHOL/MEMPHIS//TN/38163
PUBLICATION TYPE: JOURNAL
PUBLICATION: VIROLOGY, 1997, V227, N2 (JAN 20), P493-499
GENUINE ARTICLE#: WD572
PUBLISHER: ACADEMIC PRESS INC JNL-COMP SUBSCRIPTIONS, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495
ISSN: 0042-6822
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: Despite their uniform ability to bind to oligosaccharide-containing terminal **sialic** acids, **influenza** A viruses show differences in receptor specificity. To test whether agglutination of erythrocytes from different animal species could be used to assess the receptor specificity of **influenza** A viruses, we determined the agglutinating activities of a range of virus strains, including those with known receptor specificities, using erythrocytes from seven animal species. All equine and avian viruses, including those known to recognize N-acetyl and N-glycolyl **sialic** acid linked to galactose by the alpha 2,3 linkage (NeuAc alpha 2,3Gal and **NeuGc** alpha 2,3Gal), agglutinated erythrocytes from all of the animal species tested (chickens, ducks, guinea pigs, humans, sheep, horses, and cows). The human viruses, including those known to preferentially recognize NeuAc alpha 2,6Gal, agglutinated all but the horse and cow erythrocytes. Fluorescence-activated **cell** sorting analysis of erythrocytes using linkage-specific lectins [Sambucus nigra agglutinin for **sialic** acid (SA)alpha 2,6Gal and Maackia amurensis agglutinin for SA alpha 2,3Gal] showed that both cow and horse erythrocytes contain a large amount of SA alpha 2,3Gal-, but

virtually no SA2,6Gal-specific lectin-reactive oligosaccharides on the **cell** surface, while human and chicken erythrocytes contained both types of oligosaccharides. Considering that the majority (>93%) of **sialic** acid in horse and cow erythrocytes is of the N-glycolyl type, our results suggest that viruses able to agglutinate these erythrocytes (i.e., avian and equine viruses) recognize **NeuGc** alpha 2,3Gal. These findings also show that agglutinating assays with erythrocytes from different animal species would be useful in characterizing the receptor specificity of **influenza** A viruses. (C) 1997 Academic Press

6/3,AB/9 (Item 9 from file: 440)
DIALOG(R)File 440:Current Contents Search(R)

07741997 References: 30
TITLE: Sulphatide binds to human and animal **influenza** A viruses, and inhibits theviral infection
AUTHOR(S): Suzuki T (REPRINT) ; Sometani A; Yamazaki Y; Horiike G; Mizutani Y; Masuda H; Yamada M; Tahara H; Xu GY; Miyamoto D; Oku N; Okada S; Kiso M; Hasegawa A; Ito T; **Kawaoka Y**; Suzuki Y
CORPORATE SOURCE: UNIV SHIZUOKA,SCH PHARMACEUT SCI, DEPT BIOCHEM, 52-1 YADA/SHIZUOKA 422//JAPAN/ (REPRINT); UNIV SHIZUOKA,SCH PHARMACEUT SCI, DEPT BIOCHEM/SHIZUOKA 422//JAPAN/; UNIV SHIZUOKA,SCH PHARMACEUT SCI, DEPT RADIOBIOCHEM/SHIZUOKA 422//JAPAN/; GIFU UNIV,DEPT APPL BIOORGAN CHEM/GIFU 50111//JAPAN/; ST JUDE CHILDRENS HOSP,DEPT VIROL & MOL BIOL/MEMPHIS//TN/38101
PUBLICATION TYPE: JOURNAL
PUBLICATION: BIOCHEMICAL JOURNAL, 1996, V318, ,2 (SEP 1), P389-393
GENUINE ARTICLE#: VH412
PUBLISHER: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON, ENGLAND W1N 3AJ
ISSN: 0264-6021
LANGUAGE: English DOCUMENT TYPE: ARTICLE

ABSTRACT: We found, by using a virus overlay assay, that **influenza** A virus isolates bind to sulphatide (HSO3-Gal beta 1 --> 1'Cer), which has no **sialic** acid residue, and that the infection of Madin-Darby canine kidney **cells** with the human **influenza** virus A/Memphis/1/71 (H3N2) is inhibited by sulphatide. A/Memphis/1/71 (H3N2) causes obvious haemagglutination and low-pH haemolysis ofasialoerythrocytes reconstituted with sulphatide. All **influenza** A virus isolates from the species of animals so far tested bound to sulphatide. The sulphatide-binding specificity of the isolates was different from the viral sialyl-linkage specificity. **Influenza** A virus isolates also bound to galactosyl ceramide (GalCer; Gal beta 1 --> 1'Cer), as well as sulphatide, in thevirus overlay assays. In contrast. the **influenza** virus did not bind to N-deacyl, a derivative of sulphatide, glucosyl ceramide or the other neutral glycolipids tested. These results indicate that the linkage of galactose, orsulphated galactose, to ceramide is important for viral binding.

6/3,AB/10 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0301645 DBR Accession Number: 2003-03430 PATENT
New mutant **cell** for propagating **influenza** virus with decreased

sialidase activity useful as vaccine, comprises decreased levels of **sialic** acid containing host **cell** receptors for **influenza** virus - packaging **cell** culture for **influenza** A virus and **influenza** B virus infection recombinant vaccine, nucleic acid vaccine and gene therapy

AUTHOR: **KAWAOKA Y**

PATENT ASSIGNEE: WISCONSIN ALUMNI RES FOUND; KAWAOKA Y 2002

PATENT NUMBER: WO 200268632 PATENT DATE: 20020906 WPI ACCESSION NO.: 2002-706991 (200276)

PRIORITY APPLIC. NO.: US 271044 APPLIC. DATE: 20010223

NATIONAL APPLIC. NO.: WO 2002US5455 APPLIC. DATE: 20020222

LANGUAGE: English

ABSTRACT: DERWENT ABSTRACT: NOVELTY - An isolated mutant **cell** (I) comprising decreased levels of **sialic** acid containing host **cell** receptors for **influenza** virus relative to a corresponding wild-type **cell** which supports efficient **influenza** virus replication, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) isolating a **cell** that has decreased levels of receptors for **influenza** virus, comprising: (a) contacting a population of **cells** permissive for **influenza** virus replication and sensitive to lectin or agglutinin growth inhibition with an amount of lectin or agglutinin to yield **cells** that are resistant to growth inhibition by the lectin or agglutinin that specifically binds **sialic** acid; and (b) isolating a lectin- or agglutinin-resistant **cell** having decreased levels of receptors for **influenza** virus; (2) a lectin- or agglutinin-resistant **cell** isolated by method (1); (3) propagating **influenza** viruses having reduced sialidase activity by contacting (I) and the lectin- or agglutinin-resistant **cell** with an amount of an **influenza** virus having reduced sialidase activity to yield progeny virus; (4) a progeny virus obtained by method (3); (5) using a host **cell** having decreased levels of **sialic** acid containing host **cell** receptors for **influenza** virus, comprising: (a) contacting (I) and the lectin- or agglutinin-resistant **cell** with an amount of an **influenza** virus having wild-type levels of sialidase activity to yield progeny virus; and (b) serially propagating the progeny virus with (I) and the lectin- or agglutinin-resistant **cell** to yield adapted viruses that efficiently replicate in the mutant **cell** and the lectin- or agglutinin-resistant **cell** ; and (6) isolated adapted virus obtained by method (5), which does not have a mutation in the hemagglutinin (HA) gene relative to the virus having substantially wild-type levels of sialidase activity. WIDER DISCLOSURE - Eliciting an immune response to an **influenza** virus, which may be prophylactic or therapeutic for an **influenza** virus infection. BIOTECHNOLOGY - Preferred **Cell**: The mutant **cell** is a mammalian **cell**, particularly swine, bovine, simian or canine **cell**. Alternatively, the mutant **cell** is a mink lung **cell**, or an avian **cell** . The wild-type **cell** is MDCK **cell**. The mutant **cell** has decreased levels of **N-acetylneuraminic** acid and/or **N-glycolylneuraminic** acid, particularly at least 10-fold lower levels of **N-acetylneuraminic** acid and at least 2-fold lower levels of **N-glycolylneuraminic** acid relative to the corresponding wild-type **cell**. The lectin-resistant **cell** is resistant to growth inhibition by Maakia amurensis or Sambucus nigra lectin. Preferred Method: In isolating a **cell** that has decreased levels of receptors for **influenza** virus, the lectin is Maakia amurensis, Sambucus nigra or Tritrichomonas mobilensis lectin. The

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agglutinin is Limax flavus agglutinin. The lectin specifically binds **sialic** acid linked to galactose by alpha(2-3) or alpha(2-6) linkages, or to N-acetylgalactosamine by alpha(2-6) linkages. The method of using a host **cell** having decreased levels of **sialic** acid containing host **cell** receptors for **influenza** virus, further comprises isolating the adapted virus. In method (3) or (5), the **influenza** virus is particularly type A or B **influenza** virus. ACTIVITY - Virucide; Immunomodulator. No biological data is given. MECHANISM OF ACTION - Vaccine; Gene therapy. USE - The mutant **cell** is useful in propagating **influenza** virus having reduced or decreased sialidase activity. The obtained virus may be employed in vaccines, in preparing monoclonal or polyclonal antibodies specific for those viruses, in preparing recombinant or reassortant viruses, or for gene delivery including the delivery of immunogenic non-**influenza** virus proteins or peptide for vaccines or therapeutic proteins. ADMINISTRATION - The dosage of attenuated virus may range from 103-107 plaque-forming units (PFU)/kg. The inactivated vaccine can be given at a dose of 0.1-200 microg HA protein. Administration is by subcutaneous, intravenous, intradermal, intramuscular, intraperitoneal, intranasal, oral or transdermal routes. EXAMPLE - No relevant examples given.(33 pages)

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